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Physical Work Capacity in Diabetic Schoolchildren

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Physical activity is of great importance in the management of diabetic children. In an earlier investigation from this department by Larsson *et al.* [16] a tendency was found for diabetic adolescent girls to have an inferior physical work capacity in comparison with non-diabetic girls of the same age.

Lack of exercise has been supposed to promote the development of cardio-vascular damage. This problem has been studied in experimental animals as well as in human subjects, both individually and epidemiologically (for references see [16]). Some of the vascular lesions of diabetes mellitus cannot be distinguished from non-diabetic atherosclerosis [15]. It is thus possible that a low daily activity may contribute to the premature development of angiopathy in the diabetic population.

As the previous findings [16] were based on a rather small material, a test of the physical fitness of a larger group of diabetic children seemed worthwhile. The present study deals with the results of an investigation on the heart rate response to standard loads on a bicycle ergometer performed on a group of 129 diabetic schoolchildren and 123 non-diabetic controls.

Material and Methods

The 129 diabetic children who performed the exercise test comprised 78.2% of all diabetics attending the schools in Stockholm during the school year 1960–1961. For each of these children a non-diabetic control child was chosen according to the social twin principle but only 123 non-diabetics (79.4%) took part in this investigation. Before testing, each child was physically examined by the author and on the test days determination of the ESR was made in 160 (75 diabetics and 85 non-diabetics) of the final cases. The composition of the material is shown in Table 1. Owing to ESR above 20 mm/hr and/or obvious signs of acute illness four cases had to be omitted. Out of the final material 192 cases were matched into pairs. For further details concerning the material see references 19 and 20.

Later all mothers were interviewed and specially asked if their child took part in any sports and/or activities besides the regular physical education at school. Furthermore they were asked to report the ordinary daily physical behaviour of their child. This information was classified by the author into three grades: high, medium and low. Participation in physical education at school was registered and, regarding the pairs, who at the time of investigation were classmates, the school reports (converted to a point system of 1–3) distributed during the two terms of the study were compared.

All children were tested during the first

TABLE 1 *Composition of material*

	Primary material			Rejected cases			Final material		
	♂	♀	Total	♂	♀	Total	♂	♀	Total
Diabetics	63	64	129	3	3	6	60	63	123
Non-diabetics	58	65	123	—			58	63	1 1
Total	1 1	131	[illegible]	3	3	6	118	126	[illegible]

two weeks of February 1961. The investigation was performed at various times of the day and the pairs were, as far as possible, called together.

The height and weight of each child were measured before the test. Blood pressure was registered in the supine position after a few minutes' rest.

The work test was performed on an electric bicycle ergometer [1] in the sitting position. Two such newly calibrated bicycles were used.[1] The heart rate was determined by direct writing ECG[1] recording every second minute and the criteria for relatively steady state were estimated according to Holmgren et al. [11]. The subjects were tested at tw consecutive work loads six minutes at each load. The loads were chosen in advance according to earlier reports with the same method [1 , 4 6, 16, 1]. The initial load was predicted to give a pulse rate of about 130 per minute, the second of 150–1 0 per minute. To obtain two tests with sufficiently high pulse rates a few of the oldest boys had to proceed to a third load. Due to lack of steady stat the results of certain children at one of the work loads had to be rejected, but only four cases were not in the steady state at any of the loads (Table 1).

[1] Elema Corp., Stockholm.

TABLE 2 *Height weight and blood pressure among boys and girls in the various age groups*

Mean values ± standard errors of the means are given. Figures in brackets denote number of cases where these deviat from the total given. D = diabetic, N = non-diabetic

Age group, years	No. of cases D	No. of cases N	Height, cm D	Height, cm N	Weight, kg D	Weight, kg N	Blood pressure Systolic D	Blood pressure Systolic N	Blood pressure Diastolic D	Blood pressure Diastolic N
BOYS										
10	14	12	133.9 ± 1.8	140.2 ± 1.7	30.7 ± 1	31.1 ± 1.1	114	11 (11)	73	7 (11)
11 1	10	10	14 .8 ± .8	1 .07 ± .9	34 . ± 1.6	30 . ± .8	113	110		76
13–14	17	16	160.5 ± .0	163.4 ± 1.8	43.7 ± 1.4	5 .1 ± .0	122	1 3	8	73
15–16	10	8	170.2 ± .0	1 4.8 ± 2.8	56.5 ± [illegible]	5 ± 3 9	130 (9)	134	83 (9)	8
1 –20	9	11	1 6. ± 1.8	1 86 ± 1	64.2 ± .1	64.0 ± .4	141	135	83	84
GIRLS										
10	1	1	138.8 ± 1.3	140.3 ± .2	30. ± 1.0	31 . ± 1.3	1 0	110 (11)	79	6 (11)
11 1		13	1 4.1 ± .5	15 . ± [illegible]	4 .3 ± .3	41.6 ± [illegible]	1 9	1 4	87	83
13–14	15	1	1 5 1 1	16 .3 ± 1.4	49.3 ± 4.4	48.8 ± 4.3	123	123	84	83
15–16	1	1	16 .4 1.3	166. ± 1.	54.0 ± 0.8	53. ± 1.3	120	121	83	9
1 –20		9	166 .3	166.5 ± 1.4	5 .0 ± .6	53.9 ± .1	125	123	81	83
Total	123	1 1								

TABLE 3 *Heart rate at different work loads among boys and girls*

Mean values ± standard errors of the means are given. Figures in brackets denote number of cases. D = diabetic; N = non-diabetic.

Age group, years	150 kpm/min D	150 kpm/min N	300 kpm/min D	300 kpm/min N	450 kpm/min D	450 kpm/min N	600 kpm/min D	600 kpm/min N	900 kpm/min D	900 kpm/min N
BOYS										
7–10	128.1 ± 4.0 (13)	133.0 ± 2.7 (13)	140.3 ± 2.0 (12)	140.7 ± 2.4 (11)	—	151.0 (1)	—	—	—	—
11–12	—	—	137.9 ± 2.6 (9)	128.6 ± 4.6 (10)	166.1 ± 2.4 (10)	150.3 ± 5.5 (9)	—	157.0 (3)	—	—
13–14	—	—	128.3 ± 2.7 (16)	122.6 ± 4.1 (16)	148.6 ± 3.0 (17)	139.9 ± 4.3 (16)	155.6 ± 3.1 (8)	145.3 ± 3.3 (9)	—	—
15–16	—	—	124.7 ± 2.3 (10)	118.3 ± 4.1 (7)	—	—	161.5 ± 4.6 (6)	144.5 ± 6.9 (8)	171.0 (2)	159.8 (2)
17–20	—	—	117.4 ± 1.0 (8)	114.6 ± 4.4 (11)	—	—	140.8 ± 4.7 (8)	137.4 ± 2.6 (7)	159.5 (2)	160.8 ± 3.1 (5)
GIRLS										
7–10	136.4 ± 2.8 (16)	135.0 ± 2.6 (12)	152.8 ± 1.9 (13)	164.1 ± 2.3 (9)	—	—	—	—	—	—
11–12	—	—	147.0 ± 8.8 (5)	144.4 ± 1.9 (11)	164.4 ± 6.6 (5)	172.5 ± 2.7 (13)	—	—	—	—
13–14	—	—	143.5 ± 2.9 (15)	141.8 ± 5.3 (11)	166.9 ± 3.0 (14)	165.2 ± 5.5 (10)	—	190 (1)	—	—
15–16	—	—	144.5 ± 2.9 (16)	132.4 ± 3.0 (17)	—	—	177.8 ± 2.4 (15)	174.7 ± 3.3 (11)	—	—
17–20		—	133.9 ± 8.0 (7)	130.2 ± [illegible]7 (9)	—	—	172.7 ± 3.0 (6)	172.4 ± 4.6 (7)	—	—

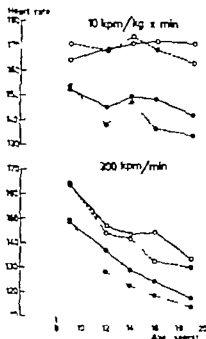


Fig 1 Physical work capacity by age and sex. The mean calculated heart rate t 10 kpm/kg body weight min is given above and the mean heart rat at a work load of 200 kpm/min below —— Diabetics; —— non-diabetics ● boys; O girls.

Results

values for height weight and blood pressure are given in Table 2. For all cases the mean values for height and weight lay well within the normal limits [8 13]. However the diabetic boys of all age groups were not as tall as and weighed less than corresponding non-diabetics. This tendency was analysed by t testing the sum of the individual differences within matched pairs. For height a significant difference ($p<0.01$) was found, and for weight a probably significant difference ($p<0.05$).

The difference in height between diabetic and non-diabetic girl was not as regular and less pronounced (p 0.1). The older diabetic girls weighed more than the control cases but neither within any age group nor for all the matched pairs did t-tests show any significant differences.

The diabetics had functional murmurs in 12.2% (4 ♂ 11 ♀) and the non-diabetics in 11.0% (7 ♂ 4 ♀). One diabetic boy had a wandering pacemaker and two non-diabetic children had isolated atrial ectopic beats. The systolic and diastolic blood pressures increased with age in both sexes and in about the same way for diabetics and non-diabetics. The highest values were obtained for diabetics 17–20 years old. Seven diabetics (4 ♂ 3 ♀) and five non-diabetics (2 ♂ 3 ♀) had a diastolic pressure of 100 or above

The heart rate response to fixed work loads is given in Table 3 and Fig. 1 In the youngest age group there was no difference between diabetics and controls In the other groups and at all loads (with an exception for 11–12 year-old girls at 450 kpm/min)[1] the diabetics had higher heart rate

The difference between diabetics and non-diabetics was examined in the matched pairs, both for each age group at each work load and for all age groups together at the different loads For boys a probably significant difference was obtained at load 450 ($\bar{d}=11.3\pm5.1$ $n=21$ $p<0.05$) and 600 kpm/min ($\bar{d}=14.5\pm5.1$ $n=11$ $p<0.02$) but otherwise there were no statistical differences. Among the girls none of the differences was significant.

The difference in weight between diabetics and non-diabetics had to be taken into account when evaluating the subjects physical fitness A work load of 10 kpm/kg

[1] kpm kilopond meter One kilopond is the force acting on mass of 1 kg t normal acceleration of gravity

TABLE 4 *Calculated heart rate at a work load of 10 kpm/kg × min.*

Mean values ± standard errors of the means. Figures in brackets denot number of cases.

Age group years	Boys		Girls	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics
7–10	152.5 ± 4.7 (11)	153.3 ± 4.4 (11)	164.4 ± 1.4 (12)	171.0 ± 2.6 (8)
11–12	145.6 ± 2.. (9)	135.5 ± 4.1 (9)	169.3 ± 5. (3)	168.3 ± 3.5 (11)
13–14	148.3 ± 2.3 (16)	147.3 ± 2.6 (16)	171.3 ± 3.9 (14)	174.1 ± 3.6 (10)
15–16	148.1 ± 2.1 (9)	136.4 ± 3.9 (7)	172.1 ± 2.3 (14)	168.9 ± 3.3 (11)
17–20	142.8 ± 3.7 (4)	134.6 ± 1.7 (7)	171.5 ± 3.7 (6)	163.9 ± 3.0 (7)
Total	148.0 ± 1.4 (53)	142.8 ± 2.0 (50)	169.7 ± 1.5 (49)	169.5 ± 1.6 (47)

body weight × min was chosen and the heart rate was calculated by intra or extrapolation in those subjects who had performed two consecutive work tests in the steady state (Table 4 Fig. 1) A t test between the total mean values gave $p<0.1$ for boys. Nor was any significant difference found among the girls. In the combined age group 15–20 years, diabetic boys had a mean calculated pulse rate of 145.6 ± 2.1 and non-diabetic boys 135.5 ± 2.0 This difference is statistically significant ($p<0.01$) In the same age group diabetic girls had a mean pulse rate of 171.9 ± 2.1 and non-diabetic girls 166.9 ± .3 ($p<0.$_)

The heart rate at standard loads can be regarded as an expression of the maximal oxygen uptake in ml/kg body weight. Åstrand [3] has presented a nomogram enabling prediction of the maximal oxygen uptake, aerobic capacity on the basis of the heart rate at fixed submaximal work loads. Although the nomogram is intended for adults (with a correction factor for the aged) it has nevertheless been pplied in the two oldest age groups in this material.

The mean max $\dot{V}_{O_2}$ ml/kg for the diabetic boys was 40.0 ± 0.9 ($n = 18$) and for the non-diabetic boys 43.6 ± 2.4 ($n = 18$) Corresponding figures for the diabetic

TABLE 5 *Heart rate at 10 kpm/kg × m n in diabetic boys and girls aged 15–20 years*

Mean values ± standard errors of the means. Figures in brackets denote number of cases.

Years	Duration		Age at onset	
	< 9	> 9	< 9	> 9
Boys	141.0 ± 3.3 (5)	149.7 ± 2.1 (9)	148.5 ± 1.9 (11)	140.2 ± 4.4 (6)
Girls	170. ± 1.7 (12)	173.9 ± 4.1 (8)	173.9 ± 4.1 (8)	170.7 ± 1.7 (12)

TABLE 6 *Frequency of participation in physical education at school*

	Boys				Girls			
	Diabetics		Non-diabetics		Diabetics		Non-diabetics	
Age group, years	Total no. of cases	Participants %	Total no. of cases	Participants %	Total no. of cases	Participants %	Total no. of cases	Participants %
7–10	15	100 0	15	100.0	17	100 0	13	100.0
11–12	11	81.8	10	100.0	[illegible]	91 7	12	100.0
13–14	17	94.1	16	93.8	15	86.7	14	100 0
15–16	9	77 8	8	100.0	21	[illegible]	16	100.0
17–20	10	50.0	10	100.0	9	44 4	8	100.0
Total	62	83 9	59	98.3	74	75.7	63	100.0

girls were 33 0±0.9 ($n=20$) and for the non-diabetic girls 35 7±1 1 ($n=19$) The difference among the boys 3 0 ml/kg or 8.3%, is not significant ($p<0\ 1$) but among the girls a probably significant difference ($p<0\ 05$) is obtained for the figure 2.7 ml/kg or 8.2%.

To evaluate the differences found in the postpuberal age groups the material was further analysed as regards age at onset [illegible]ion of diabetes and diabetic control [illegible]ed as described by Sterky *et al* [10] The calculated pulse rate at 10 kpm/kg min was chosen for this comparison in the age group 15–20 years. The degree of control was without influence in both sexes but the mean heart rate was lower in cases with short duration or higher age at onset (Table 5) As regards duration a probably significant difference ($p<0\ 05$) was found among the diabetic boys but otherwise no statistical significance was obtained.

The frequency of participation in physical education at school is given in Table 6 There is a declining tendency among the

TABLE 7 *Participation in regular exercise or sports in leisure hours and the mothers estimation of the subjects daily physical activity*

D diabetic; N = non-diabetic

Age group of material	Total no. of cases		Regular exercise or sports in leisure hours		Daily physical activity					
					High,		Medium,		Low	
	D	N	D	N	D	N	D	N	D	N
BOYS										
14	41	40	51	22 5	63.3	53.0	22.0	[illegible]	9 7	[illegible]
15–20	16	[illegible]	33.3	4 1	25.0	[illegible]	6 0	[illegible]	53.8	[illegible]
GIRLS										
7 14	4	39	23 8	35.5	66.7	61.2	9.5	20.8	23.9	17 9
15–20	31	23	18.4	7 7	16.1	17 4	3.8	[illegible]	59 1	20.6

diabetic children of both sexes. Out of the participants in school gymnastics 1*0 (60 ♂ and 60 ♀) were matched into pairs. Twenty-nine pairs had the same school reports for the autumn term and/or the spring term and are excluded from the calculations. The diabetic boys had an in significant lower mean report ($\bar{d}=0.33\pm0.17$ $p<0.1$) and the diabetic girls a higher ($\bar{d}=0.14\pm0.11$ $p<0.3$) than corresponding non-diabetics. The information on daily physical activity is given in Table 7 The change at puberty is most pronounced among the diabetics, the older group displaying less activity than the younger The participation in regular exercise or sports is fairly constant between the age groups among the diabetics but the non-diabetic girls aged 15–20 years are obviously less active than the younger girls.

Discussion

There are many factors influencing human physical fitness [6] and many ways of assessing it have been applied. The method of testing physical work capacity used in this study is well standardized and easily and quickly performed. The submaximal test was chosen though a direct determination of the maximal oxygen uptake is said to be the best indication of physical work capacity [4 17]. It should be emphasized that the level of oxygen uptake during exercise on a bicycle ergometer is dependent on the work load. As the individual variation in mechanical efficiency is small [3, 4, 5 17] the load on the oxygen transporting system can be evaluated from the work load provided it is submaximal.

Methodological differences make it difficult to compare different investigations. In order to evaluate the findings in the diabetic group a matched non-diabetic control material was therefore necessary It has been shown that the physical work capacity of schoolchildren might vary during the seasons [*] and so the study was conducted over a two-week period free from holidays.

The finding of a significantly lower height among the diabetics is in agreement with earlier reports [" 9 10 16] As in these studies the difference was most pronounced for boys It is not easy to explain this observation. The degree of diabetic control has been suggested as a cause but there was no correlation in this material between height and diabetic control.

The diabetic boys weighed less than corresponding controls which may in part be explained by the therapeutic principles [15] employed for most of the children. This has resulted in a caloric restriction, earlier reported by Sterky [18] The teen age diabetic girls were heavier than their controls which may indicate one of the therapeutic difficulties met within this age group

The heart rate at fixed work loads was higher among the diabetics (most pronounced in the years around puberty) but statistically significant differences were only obtained in a few instances The differences between diabetic and non-diabetic boys were more pronounced than between the corresponding groups of girls, and the explanation of this may very well be the lower physical activity of girls in general. As could be expected [1 –, 4] the girls had a higher pulse response than the boys t the same work load. The lowering

of the heart rate with increasing age (Fig 1) is evident in all materials The results of the two oldest age groups among the boys are less valid as the work load of 300 kpm/min in many subjects was too low to give a pulse rate sufficiently high to exclude the influence of extraneous factors.

As there were differences in height and weight between the diabetics and non-diabetics a comparison of heart rates at fixed *loads is not entirely satisfactory* Åstrand [4] has shown that aerobic work capacity in children without obvious obesity is highly correlated to body weight. Two ways of calculating physical work capacity with regard to the weight of the subject have been applied to this material. The diabetic children had higher heart rates at a load of 10 kpm/kg body weight × min and also lower predicted maximal oxygen uptake in ml/kg Both these findings indicate a lower degree of physical capacity in the diabetics. Regardless of the manner of the determination or calculation of physical work capacity diabetic ildren of both sexes showed a tendency increasing age to deviate more and more from corresponding non-diabetics. A higher level of statistical significance might be obtained with larger groups. An investigation on the adult population might also be of interest in proving the accuracy of the observed tendency

In the 15–20 years age group a short duration of diabetes and a higher age at onset resulted in better physical work capacity (Table 5) Due to the composition of the material [20] as regards age at onset and duration of diabetes it was impossible to further analyse the individual effect of these two factors on the work capacity

In no case did clinical examination reveal severe heart disease and the frequency of functional murmurs was the same in the diabetic groups as in the non diabetic. This observation is contradictory to that of White [21] who states that systolic heart murmurs are heard more often in diabetic than in non-diabetic children. No differences were found as regards blood pressure Diabetic children *show the same* correlation between physical work capacity and heart or blood volume and training improves their fitness as in non-diabetics [10]. Trained diabetic boys also have the same maximal oxygen uptake and the same blood lactate response as comparable non-diabetics [14]. Furthermore, the diabetics of the youngest age group in this material had the same heart rate during standard work as the comparable non-diabetics. Nor could any difference be found between the reports of physical education at school

These observations support the opinion that the lower physical work capacity of diabetics around and after puberty i not directly connected with the diabetic state l ut may depend on lack of training This statement is further supported by the *declining frequency of the diabetics* participation in physical education at school as well as by their own and their parents estimation of the daily amount of physical activity (Tables 6 and) The conspicuous influence of duration might be due to the ever-increasing tendency of diabetic children, regardless of the age at onset to avoid physical exercise The cause of this may be an anxiety and uncertainty of the diabetic child itself and of parents and teachers. Whether the reason is a more serious psychological disturbance of the

diabetic teenager or not remains unknown. However one result of this anxiety and lack of knowledge about the management of the disease may evidently be inferior physical fitness. Whether this inferiority is of prognostic importance as regards the child's mental health and vascular status cannot be set.

Summary

The heart rate at fixed work loads for 129 diabetic schoolchildren in Stockholm and matched controls was determined and evaluations with respect to the subjects body weight were made.

Diabetic boys were significantly shorter and weighed less than the corresponding non-diabetics. Teenage diabetic girls were heavier than the controls. After puberty diabetic boys and girls had a higher heart rate than the controls during the standard exercise tests. In this respect the diabetics and the controls in the prepuberal ages did not deviate from one another.

On the basis of the observations in this investigation and of other studies from this department it is concluded that the reason for the inferior physical work capacity of the diabetics may probably be explained by inadequate training.

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Blood Lipids in Diabetic and Non Diabetic Schoolchildren

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Marked derangements of lipid metabolism are present in untreated diabetes mellitus and are most evident as the hyperlipaemia of cases with manifest ketoacidosis. In insufficiently controlled diabetes and in the advanced stages of diabetic angiopathy hyperlipaemia has also been observed by some authors [1 3 24 33 42] although not confirmed by others [30 31 38] A causal relationship between elevated blood lipids and diabetic vascular disease may be postulated but remains to be proved.

In previous investigations interest has been mainly concentrated on the serum levels of cholesterol and phospholipids. During recent years new methods have made it possible to determine other fractions of the blood lipids as well, e.g the serum triglycerides and the free non esterified fatty acids (FFA) in plasma [14 22, 26]. These components have been studied in adult diabetic patients by Carlson & Östman [15], Mehnert *et al* [44] and Munkner [45] mong others. Less information is available as regards the blood lipids in children, diabeti as well as non diabetic [17 47 55, 50]. The aim of the present study has been to analyze the fasting levels of holesterol, phospholipids, triglycerides and FFA in the blood of a group of schoolchildren with and without diabetes.

Material and Clinical Methods

All diabetic children ttending the schools in Stockholm during the school year 1960–61 were invited to take part in the investigation. There were altogether 165 such cases, 75 boys and 90 girls. For each one f these non-diabetic control case was selected according t the "social twin principle with regard to sex, age, class at school, social status, number of siblings and dwelling conditions. W obtained 155 non-diabetic subjects (72 ♂ and 83 ♀). For different reasons (unwillingness, infections, other diseases) only 137 diabetics (83.0%) and 121 control (78 1) of those invited were included in the study (T ble 1) For further details with regard to th material see Sterky [51].

All cases were examined at Crown Princess Lovisa Children Hospital (KLB) during a two-week period in September 1960. A complet history and physical examination was obtained. Blood was drawn for the determination of serum lipids and the ESR (Westergren method), and the urine analyzed for protein, glucose and acetone. The FFA sampling was done on a later occasion in 79 subjects (43 diabetics, 36 controls). In the study of the relationship between FFA and blood sugar some additional cases from

TABLE 1. *Composition of material.*

Figures in parentheses denote cases with angiopathy

	Primary material			Rejected cases			Final material		
	♂	♀	Total	♂	♀	Total	♂	♀	Total
Diabetics	64 (12)	73 (9)	137 ([illegible]1)	5	6 (1)	11 (1)	59 (1[illegible])	67 (8)	1[illegible]6 (2[illegible])
Non-diabetics	57	64	121	1		3	56	62	118
Total	1[illegible]1	137	258	6	8	14	115	1[illegible]	[illegible]4

the outpatient clinic at KLB were also included in the study.

The age at onset and the duration of the disease in the diabetic patients are given in Tables [illegible]–3. At onset all had been hospitalized, and at the time of examination all were under insulin treatment with the exception of two cases who were in the postinitial stabilization phase. Sixty-two patients (4[illegible]3[illegible]) were treated in the diabetic clinic at KLB, the remainder at other children[illegible] hospitals or by private practitioners. The therapeutic principles followed at KLB have been described by Larsson & Ström (40) and Larsson & Sterky (38). For the evaluation of retinopathy all diabetic patients were [illegible]ined by an ophthalmologist. Microaneurysms and/or haemorrhages were found in 16 cases. A diagnosis of nephropathy, based on the presence of sporadic or permanent proteinuria, was made in one [illegible] these and in an additional five cases. The blood l[illegible]pid[illegible] of the cases with angiopathy are discussed analyzed separat[illegible]ly.

The patients were classified as regards diabetic control, not only on the basis of blood suga[illegible] and glycosuria, but also with regard to dietary habits, physical activity, ability to test the urine at home, socio-psychological stat[illegible] and general knowledge of diabetes. A point system ranging from 1[illegible]7 was used for this evaluation. The system was tested in a pilot study, in which 10 patients, selected at random, were classified independently by the three authors. The results obt[illegible]ined were extremely uniform. Applying the same principles to the rest of the material, one of the a[illegible]thors ((G.S.)) classified the patient[illegible] into three types [illegible] diabetic control: (A) E[illegible]cellent 13 cases (8[illegible] 5 ♀); (B) Fai[illegible] 63 cases (36 ♂, 27[illegible]); and (C) Poor 58 cases (18[illegible] 40 ♀). In three cases information was incomplet[illegible] and [illegible]lass[illegible]fication impossible.

Fourteen cases had t[illegible] be excluded. The reasons were *acetonuria (four cases)*, ESR above [illegible]0 mm (three cases), technical failure (four cases) and other causes (three cases).

TABLE 2. *Composition of material according to age at onset*

	Age [illegible]t onset (years)			
	0–5	6–10	≥11	Total
Boys	22	3[illegible]	10	64
Girl	22	34	1	73
Total	44	66	[illegible]7	137

TABLE 3. *Composition of mat[illegible]rial accord[illegible]ng to duration of diabetes*

	Duration (years)			
	0–5	6–10	11–[illegible]0	Total
Boys	[illegible]8	[illegible]8	8	64
Girls	43	[illegible]0	10	73
Total	71	48	18	13[illegible]

Table 4 *Analytical errors of the chemical methods*

	No. of duplicates	Ranges	Mean values	Analytical errors ( )	in %
Cholesterol mg/100 ml	35	120–270	174	±4.6	2.7
Phospholipids mg/100 ml	35	116–301	187	±7.3	3.9
Glycerides mMol/l	35	0.31–3.39	0.83	±0.049	5.9
FFA μMol/l	336	286–1976	749	±27.2	3.6

The final material thus consists of 244 cases (see Table 1) 156 of which were successfully matched int pairs of diabetic and non-diabetic cases.

Chemical methods

Venous blood, drawn in the fasting state was allowed to clot at room temperature. Serum was separated within 1 2 hours and frozen until analyzed. For the FFA determinations blood was taken separately in heparinized tubes on melting ice and analyzed the same day

Cholesterol was determined according to the method f Theorell & Widström [54] as modified by Cramér & Isaksson [19]. The phospholipids were determined according t Svanborg & Svennerholm [53], and the glycerides as glyceride-glycerol according t Carlson & Wadström [14] including the later modification f Carlson [12]. The plasma FFA were analyzed by the titration method f Dole [22] in the modification of Trout *et al* [56]. All samples were run in duplicat The analytical errors for the different procedures at our laboratory are given in T ble 4.

Blood sugar was determined according t the true glucose method of Ek & Hultman [23].

Results

Normal distribution was found for all compounds analyzed except for glycerides, where a tendency to skewness was observed as in the materials of Carlson [13] and Cramér [18]. However on testing th symmetry of our material the mean and median values were not significantly dif ferent ($P<0.5$) The values have therefore been statistically treated as if belonging to a symmetrical population.

The mean values for cholesterol, phospholipids and glycerides are given in Tables 5–7 and Fig 1 The difference between the five age groups was tested by means of analysis of variance A significant

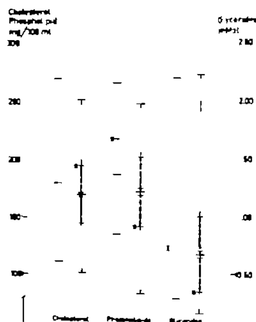


Fig 1 Serum cholesterol, phospholipids and glycerides in diabetic (——) and non-diabetic (----) groups. Ranges, mean alues ($\bar{x}$), standard errors of the means and standard deviations (s).

TABLE 5 *Serum cholesterol Mean values ± standard errors of the means expressed in mg/100 ml*

Figures in parentheses denote number of cases. *P* indicates significance between diabetic and non diabetic groups.

Age (years)	7 10	11 1	13–14	15–16	1 20	Total	
Diabetic boys	189 ± 7.5 (13)	201 ± 10.7 (10)	175 ± 8.2 (14)	148 ± 6.4 (4)	178 ± 14.5 (6)	18 ± 4 7 (47)	180 ± 3.3 (106) 31
Diabetic girl	170 ± 9.3 (17)	170 ± 8.6 (8)	183 ± 10.9 (14)	183 ± 7 7 (16)	18 ± 16.6 (4)	178 ± 4.5 (59)	
Non-diabetic boys	187 ± 8.0 (15)	183 ± 13.5 (9)	161 ± 9.2 (13)	167 ± 9.4 (8)	158 ± 4.1 (11)	165 ± 4 1 (56)	170 ± 3 (118) 4 3
Non-diabetic girls	170 ± 6.3 (17)	171 ± 11.3 (12)	180 ± 11 1 (10)	178 ± 5.6 (20)	183 ± 8.1 (8)	17 ± 4.0 (62)	

P

TABLE 6 *Serum phospholipids Mean values ± standard errors of the means expressed in mg/100 ml*

Figures in parentheses denot number of cases. *P* indicates significance between diabetic and non diabetic groups.

Age (years)	7 10	11 12	13–14	15–16	17 20	Tot l	
Diabetic boys	194 ± 7 (13)	202 ± 8.0 (10)	185 ± 8 (13)	140 ± 7.5 (4)	170 ± 11.0 (6)	185 ± 4 6 (46)	187 ± 3.0 (105) 31
Diabetic girls	178 ± 6.3 (17)	184 ± 7.2 (8)	193 ± 7.3 (14)	197 ± 8.9 (16)	177 ± 23.1 (4)	188 ± 3.9 (50)	
Non-diabetic boys	167 ± 7.9 (13)	161 ± 13.2 (9)	160 ± 8.6 (13)	157 ± 8.4 (8)	159 ± 5.2 (11)	163 ± 3.9 (36)	1 2 ± 7 (118) 30
diabetic girls	177 ± 7.5 (17)	173 ± 9 0 (12)	163 ± 11.9 (10)	183 ± 5.5 (20)	181 ± 6.3 (8)	178 ± 3 6 (62)	

P <

TABLE 7 *Serum glycerides Mean values ± standard errors or the means expressed in mMol/l*

Figures in parentheses denot number of cases. P indicates significance between diabetic and non diabetic groups.

Age (years)	7 10	11 1	13–14	15–16	17 20	Total	
Diabetic boys	0.70 0.10 (17)	0.49 ± 0.04 (9)	0.63 ± 0.03 (13)	0.82 ± 0.07 (4)	0.74 ± 0.15 (6)	0.63 ± 0.06 (11)	0.72 0.03 (103) 0.23
Diabetic girls	0.7 0.06 (17)	0.86 0.11 ( )	0.83 ± 0.12 (14)	0.83 ± 0.10 (16)	0.78 ± 0.18 (4)	0.81 ± 0.05 (59)	
Non-diabetic boys	0.64 0.10 (15)	0.73 0.07 (9)	0.64 ± 0.10 (13)	0.56 ± 0.11 (8)	0.67 ± 0.05 (11)	0.65 ± 0.04 (56)	0.65 0.03 (11 0.23
Non-diabetic girl	0.54 0.06 (1)	0.75 0.13 (12)	0.8 ± 0.05 (10)	0.70 ± 0.09 (20)	0.66 ± 0.07 ( )	0.70 0.03 (6)	

P

TABLE 8 *Serum glycerides and diabetic state.*

Cases of "excellent" control have been included in the group of "fair" control.

	Diabetic control		Glycosuria (%) in preceding 12 h urine		Fasting blood sugar mg/100 ml	
	Fair	Poor	0–0.9	≥1.0	0–200	>200
No. of cases	58	44	40	58	31	1
Glycerides mMol/l	0.67 ± 0.04	0.81 ± 0.05	0.66 ± 0.06	0.77 ± 0.04	0.62 ± 0.04	0.78 ± 0.03
P	< 0.05		< 0.2		< 0.05	

difference was found in one instance only this concerning phospholipids in diabetic boys. This finding was further investigated by t-tests between adjacent age groups. A probably significant difference ($P<0.05$) was found only between the age groups 13–14 and 15–16 years. The material was further analyzed with regard to sex. The level of phospholipids was higher ($P<0.02$) in non-diabetic girls than in non-diabetic boys and diabetic girls showed higher glycerides ($P<0.02$) than diabetic boys. However no other significant differences between the sexes were found. It thus seems justifiable to conclude that in this material, neither age nor sex had any determining influence on the serum lipids of either diabetics or non-diabetics.

Th mean values for all diabetics were then compared with those for all non-diabetics. They were higher in the former group as regards all three serum lipid components. On t-test, however these differences were found to be highly significant only for phospholipids, probably significant for cholesterol, but not significant for glycerides Similar result were obtained when the individual differences between the 78 pairs were analyzed, only that the higher level of phospholipids in the diabetics was more evident in the male than in the female pairs.

Duration and age at onset had no influence on the levels of serum lipids in the diabetic patients. Nor were there any differences between the mean values for cholesterol and phospholipids in the three groups of diabetic control. However with regard to the glycerides the mean value for patients of "poor" control was higher than those for patients of "fair" or "excellent" control, but this difference was only probably significant (Table 8). A comparison between the serum lipids and the glycosuria of the night before the blood was drawn showed no significant relationships although the mean value for glycerides was higher in patients with heavy glycosuria When the material was divided into groups of patients with blood sugars above and below 200 mg/100 ml the former had a higher glyceride level than the latter and this difference was probably significant Otherwise there was no significant correlation between blood sugar and serum lipids, and comparison between glycerides and blood sugar [illegible] a correlation coefficient $r=0.1$ [illegible]

In the 20 patients with [illegible] pathy the following [illegible]

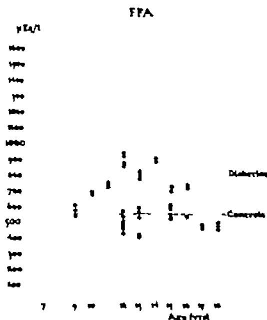


Fig — Fasting values of FFA. ● diabetics O controls ‡ mean values.

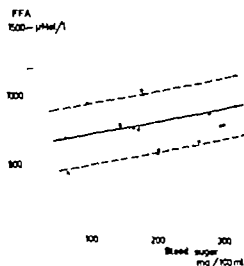


Fig 3 Correlation between FFA and blood sugar ——— regression line (Y); ——— standard deviation of Y

values were obtained. cholesterol 175 ± 8 7 mg/100 ml phospholipids 100 ± 8 0 mg/100 ml, and glycerides 0 05 ± 0 03 mMol/l. These values are apparently not different from those of the rest of the material

The results of the FFA determinations are given in Fig 2 For the diabetic patients the mean value was *815.5 ± 31.9* μMol/l and for the control subjects 585 1 ± 27.5 μMol/l. This difference was highly significant Age and sex had no influence on the FFA level in either group The correlation between FFA and blood sugar was investigated in 48 cases without acetonuria (Fig 3). On statistical analysis one obtains $Y = 1\ 017\ x + 025 \pm 225$ μMol/l, with $r = 0.32$ ($P < 0\ 05$) On the other hand, no correlation was found between FFA and glycosuria or between FFA and diabetic control.

Discussion

The levels of the blood lipids are determined by a multitude of factors e g race heredity age sex, hormones, diet physical activity season, methods of analysis [4 13 32 34 39 46] Few of the materials in the literature are uniform in these respects and any detailed comparison between the results of different investigators would therefore be of limited value

The chemical methods used by us have been discussed previously by Björntorp [10] Sunderman & Sunderman [52] among others The cholesterol method gives 4 0 % higher values than the method of Sperry & Webb according to Cramér & Isaksson [19] Our values have not been corrected by this factor a in the paper of Cramér [18]. As regards method for the determination of triglycerides most earlier workers have used indirect method that give unreliable results The introduction of th more specific methods of Carlson &

Wadström [14] and van Handel & Zilversmit [*6] have implied a great advance in this field.

Normal values for total cholesterol and phospholipids in children have previously been reported by Adlersberg *et al* [2], Dine & Jackson [21], Furman *et al* [.5] Hard & Esselbaugh [*7] Hodges *et al.* [29], Kornerup [35], Raistedt [48], Salt *et al* [50], Traisman *et al.* [55], and Wamberg [57], among others However some of the materials in these papers cannot be regarded as strictly normal, as they include hospitalized patients with various disorders or suspected somatic diseases. The average level of cholesterol and phospholipids in our control group is lower than in most of these earlier materials, although within their range The observation that neither age nor sex had any significant influence on the level of cholesterol and phospholipids in our non-diabetic children is in agreement with the results of others However in the material of Hard & Esselbaugh [*7] consisting of 48 15–16-year old boys and girls, the mean level of cholesterol was significantly higher in the girls. These authors believe that cholesterol metabolism is influenced by hormones during the adolescent period.

As regards glycerides normal values for children have been published by Traisman *et al.* [53] and by Furman *et al* [.5] The former however have not given the composition of their normal material and their mean value of 180 mg/100 ml (range 0–400) which corresponds to * 03 mMol/l, seems surprisingly high. The material of Furman *et al.* [23] covers patients of 1 –55 years of age and cannot therefore be compared with ours.

For adult Swedish subjects normal values of cholesterol phospholipids and glycerides have recently been published by Björntorp [10], Carlson [13] Cramér [18], Malmcrona [43] and Svanborg & Svennerholm [53] using th same methods as in the present study Our mean values for all three blood lipid components are lower than those given in these investigations, a finding which may permit the conclusion that an increase in blood lipids normally occurs after the end of the adolescent period One exception to this rule however is found when our mean values for glycerides are compared with those of Cramér [18]. Our value for non-diabetic boys is identical with his for men *0–40 years of age while our value for non-diabetic girls is higher than Cramér's for women *0–40 years of age

Th serum lipids in children with diabetes mellitus have previously been studied by Chaikoff *et al* [16], Danowski [*0] Dine & Jackson [21] Keiding *et al* [33], Larsson *et al* [3*], Traisman *et al* [55] and Wolff & Salt [59], among others. These authors have as a rule found significantly elevated levels only in untreated or poorly controlled ketotic patients. However values for glycerides have been given only by Traisman *et al.* [55] In the present study the only highly significant difference between diabetics and non-diabetics was f und with regard to phospholipids This observation is contradictory to those found by other workers both in children and adults with diabetes Thus the only abnormal finding with regard to serum lipids of uncomplicated patients in the materials of Adlersberg *et al* [1 3] and Carlson & Östman [15] was elevated glycerides The explanation of the *relat ve* increase in the ph spholipid in our study

is difficult The role of phosphatides in fat transport [40] should be remembered especially the observation by Ahrens & Kunkel [6] of increasing levels of phospholipids with increasing clarity of sera of high lipid content.

The absence of hyperglyceridaemia in our young diabetic patients as compared with adult diabetics might be explained by a higher carbohydrate intake in the latter [5 9] At any rate the same differences found between young and old non-diabetic subjects seem to be present in the diabetic population as well. It cannot as yet be decided whether factors other than the normal process *of ageing contribute to the* tendency towards higher blood lipids in older diabetics.

Normal values for FFA in children have previously been given by Corvilain *et al.* [17] and by Persson *et al* [47] from our department The mean values of the non diabetics in the present study are lower than those of earlier investigations, although higher than in normal adults [8, 44 45].

Laurell [41] and Dole [22] among others, have shown the close metabolic association between FFA and triglycerides. *Both these fractions are extremely eleva*ted in untreated diabetes. In controlled adult diabetics a moderate increase of FFA is still present [22 44 58] Our results in non-ketonuric diabetic children are in agreement with these previous studies The absence of increased glycerides in our *patients, in spite of their elevated FFA, may* be explained by differences in the meta bolic turnover rate of these two lipid com pounds. As the blood was drawn in the fasting state, when the effect of insulin given the previous day had almost disappeared, it seems natural to postulate that the increase of blood lipids should be most evident in the more labile FFA fraction.

The higher mean values of some of the lipid components in the diabetic cases indicate a disturbed lipid metabolism even in the controlled diabetic patient. However as shown by *Hennes & Redding* [28], among others not even a normal level of blood *lipids* excludes the presence of an abnormal fat metabolism in diabetes. It is possible that such disturbances may be better revealed by studying the blood lipids under other conditions than in the *fasting state The 24-hour variation* including the postprandial hyperlipaemia as well as long term variations in the blood lipids of the diabetic patient, may be significantly different from that of the non-diabetic [7 36]

In our material there was no obvious relationship between the serum lipid levels and age at onset, duration diabetic control, or fasting blood-sugar level. Nor was the lipid level different in the patients with angiopathy However these cases were few and their vascular lesions moderate and therefore definite conclusions about the relation between blood *lipids* and *angiopathy* are not warranted. The predictive value in the individual patients of an abnormal lipid level as part of the diabetic "malignogram" [33] cannot yet be evaluated

Summary

The fasting blood levels of cholesterol, phospholipids glycerides and free fatty acids (70 cases only) were determined in a group of 7–20- year-old school children,

consisting of 137 diabetics and 121 matched non-diabetic controls.

Age and sex were without significant influence on any of the lipid compounds. Although only a few cases of hyperlipaemia were observed, the mean values for all lipids were relatively higher for the diabetic than for the non-diabetic group (Fig 1) The differences were highly significant for phospholipids and free fatty acids probably significant for cholesterol, but not significant for glycerides.

No correlation was found between lipid levels and the age at onset of diabetes, the duration of the disease or the degree of diabetic control In a few patients with diabetic angiopathy of moderate severity the lipid values did not deviate from those of the uncomplicated cases.

When comparing the results with the findings in adult subjects an increase in blood lipids seems to occur after the end of the adolescent period in both diabetic and non-diabetic cases. The results are discussed with regard to some known and postulated factors influencing the blood level and metabolism of lipids in the normal and the diabetic population.

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Foetal Respiration

by GÖSTA ROOTH

Respiration provides the necessary amount of oxygen and eliminates the acid end products of the internal metabolism in the form of carbon dioxide. The lung therefore is the major pH regulator because the kidneys can only excrete about 1 % of the total amount of acids produced. If the same definition is applied to the foetal respiration conditions are somewhat more complicated in that the placenta is permeable to metabolic acids of the type we often call fixed metabolites, such as lactate and pyrovate as well as many others. Therefore the pattern of the foetal respiration must take into account not only oxygen and carbon dioxide but also the fixed acids as well

Rooth & Sjöstedt [18] showed that in clamped cord blood samples taken immediately after birth from normal infants with uncomplicated deliveries, there was a balance in that the foetus absorbed as many equivalents of oxygen as it excreted acid equivalents in the form of carbon dioxide and fixed acids taken together Surprisingly enough, they also found that more fixed acids than carbon dioxide were excreted, but because of the indirect way of measuring the total carbon dioxide content of the blood not too much importance could be attached to this finding

In the present study the total amounts of oxygen and carbon dioxide in the cord blood were measured by a method which was independent of the method used for measuring the fixed acids. Both methods are more direct than those used in the study cited above

Material and Methods

All the measurements were done on blood samples taken from sections of the umbilical cord clamped immediately upon delivery The blood was drawn anaerobically into syringes, the dead space of which was filled with heparine. The sampling was kindly don by the head midwif Sister Anna Greta at the Department of Obstetrics and Gynaecology Most f the mothers were given nitrous oxide during the first stage of labour In no case were signs f intrauterine asphyxia *present and none of the newborn infants* showed asphyxia. In Case 18 the mother had severe asthma and delivery took place in the 35th week. The parity of the mother the gestation time and bnormalities, such as meconium-stained amniotic fluid or slight elevation f the maternal blood pressure, as well as the stage of dysmaturity are given in Table 1

The oxygen and carbon dioxide content of the foetal blood was measured with a gas chromatograph using a modification of the

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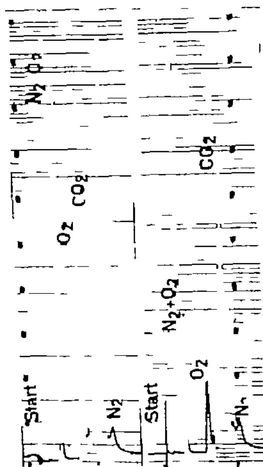


Fig. 1. Normal case Left, umbilical vein. Right umbilical artery

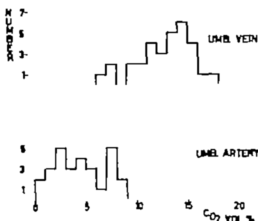


Fig. 2. Distribution of xygen content in the umbilical vessels.

technique f Muysers, Siehoff & Worth [10]. The difference in method lay in using helium as carrier gas instead of nitrogen. This necessitated the simultaneous use f a silica gel and molecular sieve column, the first column separating CO and the second separating O_2 from N according t Brenner & Cieplinski [4]. The main advantage f helium over nitrogen as a carrier gas lies in the fact that N is also analysed, as shown in Fig. 1. If any ir leaks should occur during the course f extracting the blood gases in the modified Van Slyke hamber this is mani fested in an increased amount of N and the analyses are rejected. The analyses also

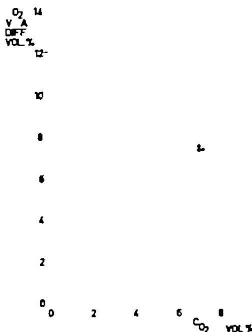


Fig. 3. Relationship between the V–A oxygen difference and the content of oxygen in the umbilical artery n cases where the V A oxygen difference does not increase with reduced oxy gen content in the umbilical artery. Most of these cases ha low oxygen content in the umbilical vein.

TABL.

Case no	C_{O_2}, vol %			C_{CO_2}, vol %				Base excess mEq/L		
	V	A_a	V-A diff	A_a	V	A V diff	R.Q	A_a	V	A V dif
1	12.8	7.3	5.5	46.3	45.8	0.3	0.06			
2	11.5	7.7	3.8	47.3	43.3	4.0	1.05			
3	6.9	0.[illegible]	6.7	39.3	35.8	3.5	0.5[illegible]			
4	14.4	2.7	11.7	56.5	43.6	12.9	1.10			
5	11.2	0.7	10.5	57.0	43.4	13.6	1.30			
6	13.5	7.7	5.8	49.0	47.3	1.7	0.29			
7	13.6	4.1	9.5	42.3	37.5	4.8	0.51			
8	14.4	7.1	7.3	35.1	33.3	1.8	0.24			
9	12.4	2.5	9.9	38.7	38.7	0.0	0.0			
10	1[illegible].0	4.8	7.2	36.[illegible]	43.7	−7.5	—			
11	9.2	3.6	5.6	45.4	32.6	12.8	2.29			
12	14.4	7.0	7.4	39.3	33.1	6.[illegible]	0.84			
13	11.4	2.3	9.1	54.8	45.4	9.4	1.03			
14	12.7	7.4	5.3	36.8	33.8	3.0	0.57			
15	11.1	5.3	5.8	29.6	27.7	1.9	0.33	−16.9	−10.5	6.4
16	13.2	6.7	6.5	34.8	29.6	5.2	0.80	−10.5	−8.9	1.6
17	6.5	1.9	4.6	35.9	24.8	11.1	2.41	−13.3	−10.0	3.3
18	10.0	—	—	—	31.3	—	—	−13.7	−7.5	6.2
19	15.4	—	—	—	34.8	—	—	−18.6	−4.3	14.3
20	10.6	1.2	9.4	42.8	33.2	9.6	1.02	−12.8	−9.2	3.6
1	8.7	0.8	7.9	37.5	31.8	5.7	0.72	−10.0	−9.5	0.5
22	12.5	2.2	10.3	41.1	37.4	3.7	0.36	−10.5	−6.7	3.8
23	16.6	—	—	—	30.0	—	—	−11.1	−6.5	4.6
24	9.9	4.0	5.9	46.0	37.6	8.4	1.42	—	—	—
25	14.3	3.6	10.7	46.7	45.5	1.2	0.11	−4.3	−2.2	2.1
26	6.2	0.4	5.8	53.0	39.3	13.7	2.36	−10.0	−8.0	2.0
27	14.7	1.7	13.0	52.4	44.8	7.6	0.58	−4.8	−1.2	3.6
28	13.3	5.0	8.3	51.0	44.1	6.9	0.84	−2.2	−2.0	−0.[illegible]
29	14.9	[illegible].4	12.5	44.5	34.6	9.9	0.79	−7.8	−4.0	3.8
30	16.1	4.0	12.1	46.9	37.6	9.3	0.77	−11.8	−9.2	2.6
31	15.3	6.2	9.1	51.6	46.5	5.1	0.56	−2.0	−0.8	1.2
32	14.3	7.0	7.3	42.2	41.8	0.4	0.06	−7.8	−6.8	1.0
[illegible]	12.3	4.1	8.1	44.1	37.8	6.2	0.82	−9.9	−6.4	3.5

come more sensitive and may be perfor ed on samples down to 0.05 ml. In the resent series the analyses were done on 5 ml samples. All values given are S.T.P. e gas chromatograph used was Perkin mer's 116E Fraktometer with a 1 meter column and a 2 meter "I" column in rallel and a thermistor detector.

pH and base excess as well as P_{CO_2} were asured by the micromethod of Astrup rgensen, Siggaard Andersen & Engel [1]. I is expressed according to NBS standards d the temperature was 37°C for all mea rements. The micro-Astrup analyses were ndly performed by the staff of the Blood Gas Laboratory of the Department of Clini cal Chemistry.

Base excess is a quantitative measurement of the non respiratory acid base balance. Base excess, which is given in mEq/L, expresses the amount of base or acid present in a blood sample in comparison with normal adult blood where by definition the value is 0. A positive base excess indicates the addi tion of base and a negative base excess indi cates the addition of acid. As the foetal blood has a non respiratory – metabolic acidosis, all the base excess values will be negative. For further details, the reader is referred to the paper by Astrup *et al.* [1].

P_{CO_2} mm Hg V	A V diff.	Effective	pH V	pH A_u	Case no.	Gestation time (weeks)	Dysmaturity stage	Parity: primiparae = P multiparae = M	Additional sedatives	Complications
					1	4	0	M		
						4	0	M		
					3	39	0–1	P	eg M	
					4	41	0	M		
					5	—	0	M		
					6	41	0	M		
					7	40	0–1	M		
					8	38	0	M		*Case 8* Meconium-stained amniotic fluid.
					9	42?	1	P		
					10	40	0	P		
					11	43	1	M		
					12	40	0	P		
					13	41	0	M		
					14	37	0	M		
38	22	16	7.29	7.03	15	41	1	P		
33	25	17	7.30	7.18	16	41	0–1	M		
46	2	0	7.24	7.19	17	38	0–1	M		
39	27	—	7.32	7.09	18	35	0	M		*Case 18* Severe asthma.
39	17	—	7.33	7.07	19	4	0–1	P		*Case 19* Initially severe em esis.
42	20	22	7.28	7.13	20	39	0	P		
49	10	8	7.23	7.19	21	41	0	P		
43	26	17	7.30	7.15	22	32	0	P		
33	11	8	7.35	7.23	23	43	—	P	eg mo	
—	—	—	7.34	7.32	24	42	0–1	M		
43	18	11	7.35	7.28	25	42	0–1	P		*Case 25* Slight hypertension.
46	19	15	7.28	7.18	26	42	0	M		
37	17	10	7.41	7.28	27	41	0	M		
33	10	6	7.42	7.38	28	41	0–1	M		
35	17	11	7.38	7.25	29	37	0	P		
40	27	19	7.28	7.15	30	39	0	P		
43	12	7	7.38	7.33	31	43	1	M		
38	9	5	7.34	7.29	32	40	0	P		
39.7	17.5	11.3	7.32	7.21						

Results

Short notes on the cases and all the results are given in Table I.

Oxygen. The distribution of the results of the measurements of the oxygen content in the umbilical vessels is given in Fig. 2. It will be seen that the oxygen content of the vein is fairly evenly distributed around a mean of 12.3 vol %. The content in the artery varies in such a way as to make the figure given by the mean of only limited value.

As the oxygen content in the artery varies more than that in the vein the V–A oxygen difference will vary appreciably and Fig. 3 shows that the V–A oxygen difference is increased when the arterial oxygen content is low, except of course when the venous oxygen content is already low. In the latter case the V–A difference cannot be high.

Carbon dioxide. There is a wide range in the CO_2 content of the umbilical vessels as shown in Fig. 4, although it is apparent

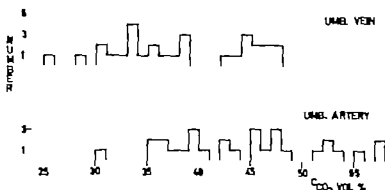


Fig 4. Distribution of carbon dioxide content in the umbilical vessels.

that the carbon dioxide content is higher in the umbilical artery than in the vein. In contrast to the range of the carbon dioxide content in the umbilical vein, the P_{CO_2} is fairly uniform, as shown in Table 1 whereas the arterial P_{CO_2} is more variable. From the analyses of the CO_2 content in the umbilical vessels, useful information can only be obtained either by studying the individual case or by taking into account some of the factors that influence the CO content.

Fig. 5 shows the correlation between the CO_2 content and the base excess and a line is drawn corresponding to P_{CO_2} 40 mm Hg This curve may be said to represent the physiological CO_2 dissociation curve of the foetal blood in the present series.

In Fig 6 the oxygen content of the umbilical artery is correlated to the A–V CO_2 difference and it will be seen that with decreasing oxygen content in the umbilical artery the A–V CO_2 difference increases.

Finally in Fig 7 the oxygen content of the umbilical artery is correlated to the A–V base excess difference. This A–V dif ference is also increased when the oxygen content of the umbilical artery is low

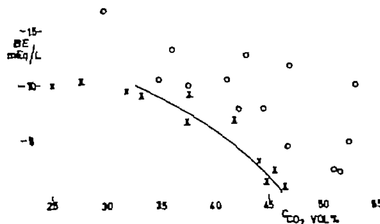


Fig. 5. Relationship between the metabolic acidosis, expressed as base excess and the total carbon dioxide content o = vein; x = vein with P_{CO_2} 40 mm Hg ± 3.

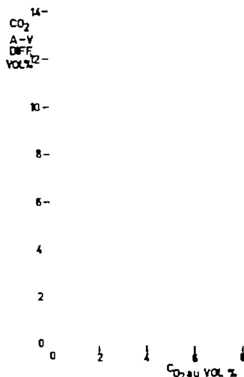


Fig. 6. Relationship between the A V carbon dioxide difference and the oxygen content of the umbilical artery

Discussion

Oxygen The oxygen content in the umbilical artery as well as in the umbilical vein is lower in the present study than in the earlier series from this hospital. The mean oxygen saturation in the vein is 56% in the present study as against 61 in the series published in 1955 (Rooth & Sjöstedt [14]) In 1955 they found a mean of 33 % in the artery whereas now it is only 18 %. Thus the artery values in particular are low The P_{CO_2} in the umbilical artery is also higher (mean value 57 mm Hg) than in the two earlier series by Rooth, Sjöstedt & Caligara [15] and Rooth & Sjöstedt [13] where it was 48 mm. The only explanation at present available for this difference is that recently the analgesia has been changed. earlier most cases were given Trilene, whereas in the present series most mothers were given nitrous oxide Further studies are in progress in order to ascertain whether this is the only reason for the difference

It will be seen from Fig 2 that most cases have the same amount of oxygen in the vein, i.e they have obtained equal amounts of oxygen from the mother through the placenta. This indicates very strongly that the oxygen supply to the foetus from the mother is not a limiting



Fig. 7 Relationship between the A-V base excess difference and the oxygen content of the umbilical artery

factor in the oxygen consumption of the foetus There is a Gaussian distribution of the total oxygen content in the vein and the oxygen content in the vein is sufficiently high to allow an extraction of quite large volumes of oxygen as the foetus can extract virtually all the oxygen from the blood A limiting factor on the maternal side is only present in those cases where the oxygen content of the umbilical vein is low In all the other cases the limiting factor for the oxygen supply to the foetus is the foetal circulation through the placenta In order to gain a sufficient amount of oxygen in spite of a reduced placental circulation the foetus must extract more oxygen from each unit of volume of blood. It follows that, given a normal oxygen content in the umbilical vein, the oxygen content in the umbilical artery is a measure of the foetal placental rate of blood flow This is demonstrated graphically in Fig 3 which shows that the V–A oxygen difference increases with decreasing amounts of oxygen in the umbilical artery If however the content of the vein is low the difference cannot be high and the values will fall outside the regression line which most of the points in Fig. 3 make The same results as those shown in Fig 3 may be obtained if the values published by Walker [19] are plotted on a similar diagram and the same effect may be observed in the study by Dawes [5] on sheep. Dawes stresses that even a small drop in the oxygen content of the umbilical artery will lead to a diminished oxygen consumption by his animals. This may very well be the case for the human foetus also. The number of cases with a high oxygen content both in the umbilical artery and vein is small and it is possible that these high values would give another steeper regression line The material is not sufficiently large for a statistical analysis in this respect

Carbon dioxide When the foetal placental rate of blood flow is slow not only must the umbilical artery oxygen content be low but also the amount of CO_2 added to each unit of blood must be high. This however is not immediately apparent from the carbon dioxide content of the umbilical artery as the amounts of fixed acids may be increased simultaneously and therefore the carbon dioxide content tends to be low because of the metabolic acidosis. That increased amounts of CO_2 are added to each unit of volume of foetal blood when the foetal placental circulation is slow is instead shown by plotting the A–V *CO_2 difference against the oxygen content* of the umbilical artery (Fig 5). The same result may be obtained by plotting the figures published by Beer Bartles & Raczowski [*] It may be deduced from Fig 4 that if all the samples from the umbilical vein were recalculated to the same Base Excess value, i e. if all lacked a variation in metabolic acidosis the carbon dioxide content in the umbilical vein would vary very little At a BE value of −6 the CO_2 content would be about 40 vol %. This is one indication that whatever CO_2 the foetus wants to eliminate has been dealt with by the placenta A stronger proof of this is to be found in the great similarity in the P_{CO_2} values of the umbilical vein the range being small and the mean identical in the present study as well as in the two earlier studies from this hospital. Finally it was earlier indicated that the oxygen supply from the

mother is not a limiting factor for the foetal oxygen supply Since CO_2 is dissol ved in the tissues about 20 times better than oxygen, once the passage of oxygen across the placenta is not limited the car bon dioxide should not be limited either

Metabolic acidosis In the present series the base excess is possibly measured with greater accuracy than in the earlier one published by Rooth & Sjöstedt [13] which included a review of the literature By measuring P_{CO_2} directly the authors had to correct the BE values obtained for the unsaturated haemoglobin by using a factor originally obtained from adult blood. In the present study all the mea surements were done after equilibrating the blood with high concentrations of oxygen at two different known carbon dioxide pressures. The base excess could then be read off directly from the diagram of Siggaard Andersen & Engel [16]. The si milarity of the results indicates that the procedure used in the earlier study was valid. The results confirm the fact that the foetal acidosis, as measured in a cord clamped immediately after delivery is im portant and of the order of 1–10 mEq/L in the umbilical vein and 2–19 in the um bilical artery in apparently normal delive ries. Because of the wide range of the results, the mean values are again of li mited use

Confirming earlier results, there is an arterio-venous BE difference which can only be interpreted as a passage of fixed acid metabolites from the foetus to the placenta. Just as the amount of CO given off per unit of volume blood must be in creased when the foetal placental circula tion is slow the same must happen to the ei l metabolites and in Fig 6 it is seen how the A-V BE difference is increased when the oxygen content of the umbilical artery is low again using this oxygen content as a sign of the slow foetal placen tal circulation.

It will be seen from the analyses of the O_2, CO and BE data that the first sign of asphyxia is a decreased rate of placental blood flow As long as this is mode rate the foetus is able to compensate by extracting more oxygen per volume and excreting more CO and fixed acids. We here find signs of the same haemodynamic changes in the placenta of man as Boeniarz & Reynolds [3] have shown in the ewe

Unfortunately we know little of the interaction between the maternal and the foetal circulation in this respect, and we know nothing of the pharmacological pos sibilities of retaining an adequate foetal placental circulation in spit of adverse factors in the mother This evidently should be a promising field for study

It is interesting to try to ascertain the level of the normal metabolic acidosis of the foetal blood. Earlier studies have shown that asphyxia and prematurity in crease the cidosis; Eastman, Geiling and DeLawder [6] James [8] Sjöstedt Rooth & Caligara [15] and several others A study of the present series shows that of the 8 cases where BE in the umbilical vein was — or lower not less than 5 cases pre sented some sort of bnormality such as prematurity maternal hypertension or suspected toxicosis.

In the asphyxiated infant the anaerobic metabolism is an obvious explanation for the foetal metabolic acidosis. But it is not known whether anaerobic metabolism is the only explanation of the foetal meta boli acidosis. One point gainst such an

explanation is that lactic acid only explains part of the total metabolic acidosis (Rooth & Sjöstedt [13]).

To return to Fig 3 it can be stated that those cases falling below the regression line have not obtained sufficient oxygen, i.e. they must at least partially have had an anaerobic metabolism at the time the sample was taken. Six cases on which BE was measured fall below the line and the mean BE in these cases is −9 0 (range −6.7 to −10 5) in the vein and −12.3 (range 10 0 to −16.9) mEq/L in the artery In the 8 cases falling close to the line the corresponding values are −4.5 (range −0.8 to −9.2) and −6 4 (range −2 0 to −11 8) Thus if we eliminate one group of cases which judging by the oxygen analyses must have a manifest hypoxia although it is not severe enough to be clinically discernible less metabolic acidosis is found.

If the metabolism is aerobic and the foetus is in a steady state, there should be a balance in that the amount of oxygen absorbed should be equal in equivalents to the amounts of carbon dioxide and fixed acids.

In the six cases with established oxygen deficiency the following balance is found in mEq/L.

V-A O diff		A V CO_2 diff		A V BE diff
3 3	~	3.4	+	3.3

Against 3.3 mEq/L O_2 as much as 6.7 mEq/L of acids are found. In the 8 cases where the oxygen supply was probably sufficient the corresponding figures are 4.4 ~ 2 6 + 1 9 i.e. 4 4 mEq/L of O_2 is balanced against 4.5 mEq/L of acids. By such a process of elimination the normal foetal metabolic acidosis might be found to be about BE −3 to −4 in the vein and BE −5 to −6 in the artery and it seems possible that this is a foetal metabolic acidosis which is *not due to anaerobic* metabolism.

Respiratory quotient. It has been shown that the arterio-venous oxygen and carbon dioxide difference varies with the foetal *placental circulation time. If the foetal* respiratory quotient (carbon dioxide production/oxygen consumption) is calculated, widely varying values may be obtained. The oxygen V–A difference is limited *to the maximum* of the total venous oxygen content and even in cases *showing* no clinical signs of asphyxia this may be low as has already been demonstrated. No similar limitation is known about the *A–V CO_2 difference. It follows* that the lower the oxygen content of the umbilical artery and the more hypoxic the infant the higher the RQ should be If 6 vol % or more of oxygen in the umbilical artery is chosen as a normal umbilical artery oxygen content, there are 8 cases in the present material with a mean V–A difference of 6 6 vol % of oxygen and 3.3 vol % of carbon dioxide This gives a mean R.Q *of 0 50* The mean RQ in the 13 cases with less than 3 vol % of oxygen in the umbilical artery is 1 06 It is perhaps even more illuminating to take the group already discussed above which was segregated as having an oxygen lack because they fell below the regression line in Fig. 3 The mean RQ in the 11 cases with an oxygen lack thus defined is 1 13 as against 0 56 in the 17 cases falling on the regression line. The cases with a high RQ are not in a steady state as shown above in the balance studies. A calculation of the balance for the cases with more than

6 vol % of oxygen in the umbilical arteries gives in mEq/L.

$$\underset{3.4}{\text{V A } O_2 \text{ diff}} \sim \underset{1.6}{\text{A V } CO_2 \text{ diff.}} + \underset{1.3}{\text{A V BE diff.}}$$

which is as good a balance as can be expected as the BE here only is known in three cases but the O_2 and CO_2 figures are from 9 cases. The difference from the former balance lies mainly in the level of the values which is due to the higher rate of the foetal placental circulation. It follows that the foetus in a steady state has an R.Q. of the order of 0.6. Several reasons substantiate this result.

1. The passage of fixed acid metabolites from the foetus to the placenta will probably contain many acids which are not decarboxylized.

2. If the foetal intermediate metabolism only partially proceeds to the CO_2 end stage intermediate acid metabolites would be eliminated from the cells to the blood and this would explain the metabolic acidosis.

3. Foetal blood has less carbonic anhydrase than adult blood. If the foetus does not have to eliminate great amounts of CO_2, less carbonic anhydrase would be needed.

Furthermore it could be an advantage to the foetus to lose some energy rich metabolites to the placenta as it does not have to keep up its own temperature. Finally, adult man breathing with his lungs, cannot eliminate acids to any large extent except through the lungs, i.e. in the form of CO_2. The foetus, however having as it were a tremendous kidney in the form of the placenta, can eliminate other acids.

It should be remembered that this speculation as to the explanation of the low R.Q. is purely hypothetical but if no other explanation will be found the low R.Q. is a sign of a difference in intermediate metabolism. Facts will have to follow from detailed analyses of the intermediate metabolism, and such studies are in progress.

The effective P_{CO_2} gradient across the placenta. The P_{CO_2} gradient across the human placenta has recently been studied by Rooth, Sjöstedt & Caligara [15] and by Prystowsky, Hellegers & Bruns [11]. The latter group only had four normal cases and record a pressure drop between the umbilical artery and the intervillous space of 8 mm Hg. Rooth *et al.* found a mean of 7 mm Hg. If a pressure gradient of somewhat less than 10 mm Hg is accepted as the actual gradient, this does not immediately give any information about the pressure gradient which is effective in pushing CO_2 from the foetal to the maternal circulation. In order to obtain the effective pressure some further treatment of the data is needed, in order to correct for the P_{CO_2} changes due to the difference in metabolic acidosis between the umbilical vein and the umbilical artery. In other words, the P_{CO_2} of the umbilical artery is higher than that of the umbilical vein, partly because of a higher total CO_2 content and partly because of a lower pH due to higher concentrations of metabolic acids.

The study of Rooth *et al.* [15] indicated that the P_{CO_2} in the intervillous space and the umbilical vein was identical. However as they did not make simultaneous measurements, some difference might have been missed. Prystowsky *et al.* [11] in their four cases found a difference of 6 mm

Hg between the umbilical vein and the intervillous space. This would leave a pressure drop of only 2 mm Hg between the umbilical artery and the umbilical vein. As will be shown, such a pressure drop is explainable on the basis of the change in metabolic acidosis. And when CO_2 is eliminated, the pressure must drop too *A total drop of 2 mm is not sufficient for* these two components. It will therefore be assumed—and this is also likely on the basis of the solubility of CO_2 in the tissues —*that the P_{CO_2} is the same in the umbilical vein of the foetus as in the intervillous* blood of the mother The actual pressure gradient is then given by the P_{CO_2} difference between the umbilical artery and the umbilical vein It remains to calculate how much of this pressure is effective and how much is 'lost' due to changes in base excess. This may best be explained by taking an example.

In Case 20 from Table 1 we find an arterial P_{CO_2} which is high i.e. 70 mm Hg, and a normal venous P_{CO_2} of 42 mm Hg The actual difference is 28 mm Hg Now in this case the foetal arterial blood has 3 6 mEq/L more fixed acids than the vein. When these acids have left the artery the pH value has increased. This is best understood by a study of Henderson Hasselbalch's equation.

$$\mathrm{pH} = \mathrm{p}K + \log \frac{Bicarb}{k \cdot P_{CO_2}}$$

where Bicarb $+k\ P_{CO_2}$ = Total CO_2. From this it is apparent that given a certain amount of total CO_2, P_{CO_2} must decrease when pH increases.

The P_{CO_2} change due to the pH change may be obtained from the nomogram of Siggaard Andersen & Engel [16] in the following way: in the course of measuring the base excess of the artery a line is drawn uniting two measured pH values obtained at two different known P_{CO_2} values. From this line BE −12.8 *is read off. In order to* find the new BE line needed for the calculation of P_{CO_2} it is not sufficient to add 3 6 mEq the change in BE due to a change in haemoglobin saturation must also be taken into account. With a haemoglobin of 16 1 g %, an oxygen saturation in the umbilical vein of 60 % and in the umbilical artery of 20 %, we find that the difference in oxygen saturation *decreases* the BE 1 6 mEq $(16\ 1 \times (60-20) \times 0.3 = 1\ 6)$ The required BE should then be increased 3 6 due to changes in fixed acids and decreased 1 6 because of changes in oxygen saturation. The resultant total change in BE is +2.0 and a new line is drawn in the nomogram parallel to the first but 2.0 BE higher Now the pH difference between these two BE lines is read off from the pH scale on the nomogram In our example the pH change is found to be 0 03 pH units. Then 0 03 should be added to the initial pH of the artery giving us 7 16 Taking account now of the oxygen saturation of the umbilical vein we obtain the P_{CO_2} in the usual way from the new BE line and the new pH. In our example the result is 65 mm Hg The difference between the recalculated arterial and the original venous P_{CO_2} (23 mm Hg) is called the effective P_{CO_2}

Carbon dioxide and oxygen diffusion coefficients across the placenta When the total amounts of CO_2 crossing the placental barrier are known, an estimate may be obtained of the amounts of CO_2 eliminated per unit of pressure gradient The mean CO_2 difference is 6.3 vol % in the cases where

the P_{CO_2} was measured and the mean effective P_{CO_2} gradient is 15 mm Hg Thus about 0.4 vol % of carbon dioxide is *eliminated per mm of pressure gradient.*

Corresponding figures for oxygen cannot be directly obtained from the present study as they necessitate the measurement of intervillous P_{O_2} umbilical artery and umbilical vein P_{O_2} However the latter may be calculated from the oxygen dissociation curves by Rooth Sjöstedt & Caligara [14] and the intervillous P_{O_2} may be taken from the paper by Sjöstedt Rooth & Caligara [17]. The mean umbilical artery P_{O_2} *is found to be 14 mm Hg and* the mean umbilical vein P_{O_2} [illegible]5 mm Hg and the intervillous P_{O_2} 40 mm Hg Taking as pressure gradient the difference between the P_{O_2} of the intervillous blood and the mean between th arterial and venous P_{O_2} the oxygen pressure gradient is found to be 20 mm Hg The mean V–A O difference in these cases is 8.1 vol %. Thus about 0.4 vol % of oxygen diffuses across the placenta per unit of pressure gradient. *The solubility of oxygen being* lower than that of carbon dioxide it might be expected that the diffusion capacity for oxygen would be much lower than that for carbon dioxide However the similarity of the values found can be explained by assuming that the carbon dioxide diffusion is not limited to the actual value found but might increase if more CO_2 were produced by the foetus. The figure for the oxygen diffusion would then be more *representative of the placental diffusion capacity* and it may therefore be justifiable to discuss the errors in order to ascertain whether the result can be considered representative or not.

In the estimation of th volume of oxygen which diffuses under physiological circumstances there is no important error The oxygen tension values may be somewhat different but the net effect on the gradient will not be much influenced by the absolute values The largest error lies in the intervillous P_{O_2}.

For a definite understanding of the diffusion, the time factor must also be taken into account and to calculate the diffusion coefficients across the placenta it is necessary to know the rate of blood flow either in the maternal or preferably in the foetal placental circulation or the oxygen consumption of the foetus The dimension for the diffusion coefficient are volume per unit of time and unit of pressure drop The unitary system generally adopted for the lung diffusion is ml/min / mm Hg [illegible] the lung the diffusion coefficient [illegible] order of 27

Bearing in mind the uncerta[illegible] figures for the foetal circ[illegible] at by Rooth & Sjöstedt [illegible] them in order to obtain a[illegible] figure for the oxygen diff[illegible] They found the foetal [illegible] the placenta to be abo[illegible] foetus of 3 5 kg. This [illegible] oxygen diffusion coefficient [illegible] mm Hg With due regard [illegible] of the same order [illegible] for the lung

Wulf [20] recent[illegible] mary of his theor[illegible] of the human placen[illegible] he arrives at somewhat lower [illegible] ml mm mm Hg For the [illegible] of the oxygen pressure gradient [illegible] a much more elaborate test [illegible] ming a [illegible] urrent between [illegible] foetal and the [illegible] nal circulation [illegible] placenta be [illegible]

the pressure difference by use of the Bohr equation. He arrives at a pressure gradient of 27 mm whereas a value of 20 mm was found in the present series and 18 mm by Sjöstedt Rooth & Caligara [17] For the calculation of the oxygen consumption Wulf and Rooth & Sjöstedt have used the same figure taken from the work of Metcalf Romney Swartwout, Pitcairn Lethin & Barron [9]. It follows that in whatever manner the oxygen pressure gradient is calculated fairly similar results are obtained and it may therefore be stated that the order of magnitude of the diffusion coefficient in the human placenta is about 1 ml O_2/min mm Hg

When the V–A oxygen difference in the foetus is of the order of 6–7 vol %, the difference in fixed acids is about 1 5 mEq/L. Assuming again a circulation *rate of 300 ml/min, the foetus* would excrete a total amount of about 00 mEqv acid per 24 hours. It is interesting to note that this amount is greater than the capacity *of the maternal kidneys for eliminat*ing fixed acids and the foetal acids must therefore be metabolized by the mother

The carbon dioxide dissociation curve The traditional way of presenting a carbon dioxide dissociation curve is to plot P_{CO_2} against total CO_2. Eastman, Geiling & DeLawder [6] showed that the *foetal* curve was lower than the maternal or in other words they showed that the foetal blood at any given P_{CO_2} contained less CO_2 than the maternal. This of course is explained by the foetal non respiratory acidosis Because this acidosis varies the carbon dioxide curves must vary too Eastman *et al* [6] for their curve used blood from 5 normal cases. They also showed that 7 individual cases were all on different dissociation curves, as did Haselhorst & Stromberger [7].

The line drawn in Fig 4 may be said to represent the *in vivo* physiological CO_2 dissociation curve in the umbilical vein at P_{CO_2} 40 which typifies most venous samples. In contrast to the oxygen *in vivo* dissociation curves by Rooth *et al* [13], these carbon dioxide curves have been obtained without any recalculation

By using the nomogram of Van Slyke & Sendroy [16] the total CO_2 content of a blood sample may be used to calculate the total CO_2 of serum. And the total CO_2 of serum may be correlated to Base Excess by the use of the nomogram of Siggaard Andersen & Engel Thus, by a combination of these two nomograms BE may be correlated to total CO_2 in whole blood. If such a line were drawn for P_{CO_2} 40 using the mean Hb values *of the present series*, this line would fall close to the present line This indicates that the adult and the foetal carbon dioxide dissociation curves *only differ because of difference* in metabolic acidosis

Summary

In 32 cases the oxygen and carbon dioxide content of the umbilical vessels was analysed. In 17 of these cases pH P_{CO_2} and non-respiratory acid base balance was also studied. The results show that the placenta even at the final stage of delivery is effective as regards O_2 and CO_2 diffusion. The umbilical artery oxygen content is a measure of the foetal placental rate of blood flow The first signs of asphyxia is a slowing of the foetal placental rate of blood flow By a simultaneous study of the values for the blood gases in the um

bilical vein and in the umbilical artery an integrated analysis may be obtained which permits an understanding of the otherwise apparently random variation of the results. In cases with high rate of blood flow the foetal respiratory quotient is low about 0.5 indicating that the foetal intermediate metabolism differs from the adult. In foetuses with an insufficient oxygen supply the R.Q is higher usually more than 1 0 Approximate figures are given for the placental oxygen and carbon dioxide diffusion coefficients.

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Salicylate Induced Malformations in Mouse Embryos[1]

by K. SUNE LARSSON HARRY BOSTRÖM and BIRGITTA ERICSON

Introduction

A long list of teratogenic agents in mammals is given in a recent review by Kalter & Warkany [8] Among the known teratogens, cortisone [7] and salicylates [18] are of particular interest, because of the extensive therapeutic use of these drugs and numerous closely related com pounds

Many studies of mammalian embryonic tissues indicate that, in comparison with adult tissues, their content of acid mucopolysaccharides is very high as is the rate of synthesis of these substances [3] It is also a well-established fact that both cortisone and salicylates inhibit the rate of synthesis of acid mucopolysaccharides *in vitro* and *in vivo* [4 5 6 11 12 17 19 20]

Since the presence of mucopolysaccharides in embryonic tissues might have an important function in growth and differentiation [1], it seems plausible to infer the existence of a relation between the teratogenic action of drugs like cortisone and salicylates, and their inhibitory effect on mucopolysaccharide synthesis. Strong evidence in favour of this view has been given by the results of recent studies by one of us on cortisone-induced cleft palate in mice and its relation to S^{35} sulphate incorporation in the mucopolysaccharides of the palatine shelves [9 10]

On the basis of the aforementioned considerations it seemed worth while to study in some detail the teratogenic action of salicylates in mice. Since some observations made in the course of this study might be of interest in the discussion of the pathogenesis of certain drug induced malformations in man [2, 13 15 16], a brief preliminary report of them is given in the following

Experimental

Primiparous mice of the A/Jax strain were injected intramuscularly with single doses of 10 mg of sodium salicylate in 0.1 ml of distilled water on various days of pregnancy (Table 1).

The embryos were removed on the 18th day of pregnancy (the day on which vaginal

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TABLE 1 *Summary of congenital malformations in embryos from pregnant A/Jax mice given an in. i jection of 10 mg of sodium salicylate on the 12th or 13th day of gestation*

Animal	Gestation day injected	No. of implanted embryos	No. of living embryos	No. of resorbed embryos	No. of living embryos with reddish-brown spots on nose or hin	No. of living embryos with reddish-brown spots on paws
1	1	7	4+1	2	3	+ 1*
2	12	8	7	1	6	1
3	1_	8	8	0	1	0
4	12	10	0	10	—	—
5	13	9	8	1	0	0
6	13	7	3	4	0	

Late death. The embryo with concurrent malformations of both hind paws is hown in Fig 3.

plug was observed being denoted as the zero day of pregnancy), and inspected for external anomalies. The embryos were also taken for sectioning and staining (Weigert-van Gieson) as well as for skeletal staining f whole embryos with Alizarin red S.

Results

As seen in Table 1 a high incidence of external anomalies was found among em bryos from the 6 mothers given sodium salicylate on the 12th or 13th gestation



FIG. 1 Four 16 day embryos from litter of 7 living, whose mother was given 10 mg of sodium salicylate in. on he 12th day of pregnancy (animal 2 in T ble 1) The three embryos on the left show the characteristic reddish-brown spot on the nose of varying extent The embryo on the extreme right has similar spot on its left front paw



Fig. — Two 18-day embryos from litter of 4 living whose mother was given sodium salicylat as the mother in Fig 1 (animal 1 in T ble 1) The left embryo shows reddish-brown spot on both the nose and the right hind paw The right embryo has no external anomalies.

day The most striking of these malformations was the appearance of reddish brown spots on the nose chin and paws (Figs. 1 and 2) present in 14 of 31 inspectable embryos. Histological examination of these discoloured tissues revealed a large mass of blood enclosed in a thin walled capsule



Fig. 3. This embryo was found dead on the 18th embryonic day and was a litter mat t the embryos in Fig 2. Both hind paws show gross anomalies, and reddish-brown spot is seen on the left front paw

In one embryo with a spot on the left front paw both hind paws showed gross malformations as seen in Fig 3

As will be reported in detail elsewhere skeletal staining of whole embryos from this group of mothers, as well as from 18 mothers injected on the 7th, 8th 9th 10th and 11th gestation day showed a high incidence of deformities of ribs and vertebrae This applied particularly to offspring of mothers given an injection on the 9th day

Discussion

A feature of particular interest in this study was that the aforementioned malformations appeared in either vascular or skeletal tissues, both known to contain acid mucopolysaccharides [14].

Vascular changes localized in distal parts of the limbs might be followed by maldevelopment of the paws [21] The occurrence of a severe malformation of both hind paws and of a vascular lesion

of one of the front paws observed in the same embryo indicates this sequence of events. Furthermore, it seems reasonable to suggest that more severe deformities of the extremities, such as hemimelia and amelia would arise as outlined above if vascular changes of the type described were to occur at earlier stages of development.

The remarkable localization of vascular changes on the nose found in this investigation does not seem to have been reported in earlier studies on teratogens of these types. On the other hand, these findings recall the preliminary descriptions given in the literature of the "Schnurrbarten haemangiomas" described in the "thalidomide syndrome [2, 13 15 16].

On the basis of the present results in addition to the fact that salicylates are commonly used drugs, of which easily resorbable types have been introduced on the market in recent years, it seems justified to devote continued interest to the possible role of salicylates as teratogenic agents even in human subjects

Summary

A single intramuscular injection of 10 mg of sodium salicylat was administered to pregnant mice of the A/Jax strain on one of the 7th to 13th days of gestation. A preliminary report is given of the gross anomalies observed in dissected out 18-day embryos. They consisted of severe disturbances in skeletal and vascular development The embryos seemed to be most sensitive to injection given on the 1*th and 13th days of gestation.

The possible relation is discussed between development of these anomalies and inhibition of mucopolysaccharide synthesis by salicylates

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Studies in Oligophrenia

II Amino-Aciduria in Mentally Deficient Children

by H. H. VAN GELDEREN and L. J DOOREN

Introduction

The interest in inherited disorders of metabolism in mental deficiency has greatly increased during the last decade The known hereditary diseases of metabolism have been extensively reviewed recently [12, 20]. Many of them as summarized by Paine [17] are associated with mental defect A large number of inherited disorders of metabolism are characterized or accompanied by hyperaminoaciduria [3 9 19], whereas many of these are also associated with mental defect [11 17]. Therefore the screening of mentally defective children for bnormal amino-acid excretion is becoming an important method in discovering metabolic disorders of probably inherited origin.

Several investigators have used paper chromatography in studies mong mentally deficient patients. Though a few abnormalities have been found [11 17 23] this kind of study has been cumbersome and not very fruitful.

Ghadimi s [9] quick screening method was not reliable in our hands.

In the following study we have measured the free alpha-amino-nitrogen excretion in 131 mentally deficient children according to diagnosis In this way we have tried to correlate clinical diagnosis and possible metabolic disorders, or in other words to concentrate the suspects of hyperaminoaciduria out of a large group of oligophrenics.

Material and Methods

The following groups were composed from the classification we have used in studying medical aspects of mental retardation in 550 children 3–17 years of ge of whom 384 could be classified. Criteria for classification have been discussed in an earlier paper [7]

1 Mild familial[1] oligophrenia (IQ > 0)

Familial severe oligophrenia (imbeciles and idiot) without congenital malformations (excluding phenylketonuria).

3 A group of patients with familial ligophrenia in which it was not possible

[1] That is, one or more cases of oligophrenia among siblings or parents.

to decide with certainty whether they belonged to group 1 or group 2.

4. Oligophrenia with (multiple) congenital malformations (excluding mongolism). This group is heterogeneous: the multiple congenital malformations point to prenatal lesions or anomalies of the brain as the cause of mental defect. In this group may be found cases of genetic defects as well as cases of embryopathy, fetopathy or chromosomopathy.

5. Cerebral damage of perinatal or postnatal origin.

The children in whom aminoaciduria was determined have been chosen from these groups without selection.

All patients were on the same normal diet, which was frequently checked. Patients who were ruminating or patients with cachexia, acute diseases, hormone medication or hypothyreosis were excluded. Twenty four hour specimens of urine were collected if possible. If not possible part of a 24-hour collection or a morning sample was used for analysis. All urines were analyzed immediately after collection or stored at -4°C. The analysis was repeated at random (with intervals from 1 week to 1 year) in a number of patients to measure the constancy of aminoaciduria. Free alpha-amino-nitrogen in urine was determined by the titrimetric ninhydrin CO_2 method [18]. All analyses were performed by the same technician. Total nitrogen in urine was determined by the Kjeldahl method. Creatinine in urine was determined by the method of de Vries & Daatselaar [see 10]. Normal values for alpha-amino-nitrogen excretion in our laboratory have been determined in 31 children 3–17 years of age and 11 young adults.

Expression of aminoaciduria

As the amount of free alpha-amino-nitrogen excreted daily varies with age [1, 9], this way of expression is of no use in comparing groups of children of different ages. In calculating the excretion per kilogram body weight per day several authors found a fairly constant value for children from ½–13 years of age [1, 2, 13], independent of sex [2] and with perhaps a slight rise during puberty [7]. Correct 24-hour collection of urine is necessary.

Most investigators express the alpha-amino-nitrogen excretion as a percentage of the total nitrogen excretion [1, 5, 13, 14]. According to Jagenburg [14] morning samples of urine may be used for calculation of this index. This finding is of course of great advantage in studies of mentally retarded children, in whom 24-hour urine samples are often impossible to obtain. We have also compared amino-acid excretion in morning samples and 24-hour samples in 20 children 2–14 years of age. The mean index

$$\frac{\alpha AmN}{\text{total N}} \times 100\,\%$$

in these morning samples was only 0.12 % ± 0.02 % lower than in the 24-hour samples of the same day. This agrees completely with Jagenburg's findings. The index

$$\frac{\alpha AmN}{\text{total N}} \times 100\,\%$$

is therefore of great advantage in studying the alpha-amino-nitrogen excretion in mentally retarded children. The main ob-

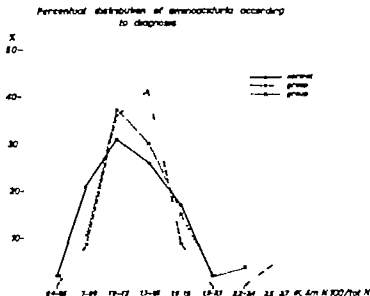


Fig. 1

jection to its use is the influence of the protein intake on both the alpha-amino-nitrogen and total nitrogen excretion. All children were, however on a well-controlled, unrestricted diet and under these circumstances the index has been found to be very constant [1 13]. This was also obvious from our duplicate samples (see further)

Some authors [6 9] use the index αAmN/creatinine J genburg [14] calculated normal values on the basis of creatinine excretion in children as measured by Stearns [21] He found an index rising with increasing age. Using more recent determinations of normal creatinine excretion in children [4] however we found fairly constant normal values for this index in children 4–13 years of age Nevertheless, we consider this index less reliable for expressing the alphaaminonitrogen excretion in our patients for several reasons.

Whereas creatinine excretion has always been considered as very constant even from hour to hour in one individual, recent reports [22] suggest great variations in some individuals Secondly the frequent abnormalities of muscular function in our patients may have a profound influence on creatinine excretion. In our patients we have indeed found a large variation (from 10 1–26.5 mg/kg/24 hr) while the average creatinine excretion in 16 patients was 20–25% lower than the average values given by Clark [4]. Thirdly the creatinine excretion in boys and girls shows increasing differences from the onset of puberty causing a distinct sex-difference between the indices αAmN/creatinine in boys and girls

Therefore we have used the index

$$\frac{\alpha AmN}{total\ N} \times 100$$

calculated from 24-hour collections or

TABLE 1 *Excretion of αAmN in mentally deficient children according to diagnosis*

Diagnosis group	αAmN/tot.N 100				αAmN/kg/24 hr (mg)		
	Number	Mean	S.D	% > 1.8	Number	Mean	S.D.
1	23	1.34	0.073	5	20	2.73	0.20
2	[illegible]	1.62	0.094	27	11	2.86	0.25
3	9	1.51	—	22	5	3.04	—
4	15	1.47	0.064	4	9	2.77	—
5	46	1.30	0.056	6	27	2.89	0.18
Total	131				72		
Normal	4[illegible]	1.22	0.030	3	29	2.94	0.19

S.D = standard deviation of the mean.

morning samples of urine. If a 24-hour sample of urine could be obtained, the alpha-amino-nitrogen excretion per kilogram body weight per day was also measured. In a number of patients the creatinine excretion was determined as well, but we did not use these data in our study

Results

The results of our study are summarized in the tables and figures It can be seen that the patients with mild oligophrenia (group 1) and with brain damage during and after birth (group 5) show normal amino-acid excretion The mean values do not differ significantly from our normal values.

The mean value for amino-acid excretion is significantly higher ($p<0.001$) in group 2 in which group one would expect theoretically to find the children with inborn errors of metabolism Patients with

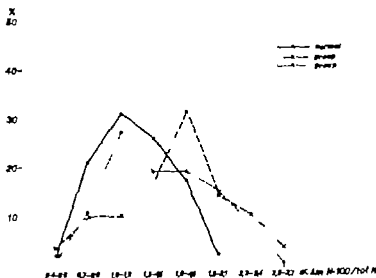


Fig. 2.

TABLE 2 *Repeat examination for amino-acid excretion expressed as αAmN × 100/tot N*

Number of pairs	Mean of first analysis	Mean of second analysis	Mean of differences (absolute values)
15	1 66	1 71	0.15

phenylketonuria and hypothyroidism have been excluded from this study In group 2 not only is the incidence of hyperamino-aciduria highest (97 %) but also the whole frequency distribution curve is shifted to the right (Fig. 2)

As group 3 is composed of patients belonging to either group 1 or 2, the values for α-amino-nitrogen excretion lie between those of group 1 and 2.

The children with oligophrenia associated with other congenital defects (group 4) show a rather high amino-acid excretion, significantly higher than normal ($p < 0\ 01$) We could find no differences in this respect between familial and isolated cases within this group, further studies in a larger number of patients may clarify the cause of the high amino-acid excretion. The frequency distribution curve reflects the more heterogenous composition of group 4.

There was in general a good correlation between α-amino-N excretion expressed as mg/kg/24 hr However variations of the latter were larger

In the 15 cases with repeated determination of amino-acid excretion (intervals varying from 1 week to 1 year) no significant differences (Wilcoxon pairs test) were found between first and second examinations (Table)

This makes an influence of variations of daily diet upon the index most unlikely and shows the constancy of the index used Th same was true for the nine duplicate determinations in which the excretion could be measured as αAmN/kg/24 hr As mentioned earlier there are good reasons for not using the index αAmN/creatinine per 24 hr in mentally deficient children. In 22 cases we have compared the αAmN/tot.N index with the index αAmN/creatinine per 24 hr and αAmN/kg/24 hr A correlation was found (Table 3) but variations were wide.

As Berger found an increase of amino-

TABLE 3 *αAmN/creatinine excretion per 24 hr compared with αAmN/kg/24 hr and αAmN 100/total N in 22 patients*

		Mean $\frac{\alpha AmN}{creatinine}$ 24 hr	Number of patients
$\frac{\alpha AmN}{tot.N}$ 100	< 1.8	0 18	15
	1.8	0.26	7
αAmN/kg/24 hr	3 0	0.17	9
	3 0–4 0	0 21	9
(mg)	4 0	0 30	4

aciduria in puberty we have also compared the values in our patients before and during puberty However no influence of age was found.

A considerable number of our patients was treated with anti-convulsant drugs or with phenothiazine derivatives. As the latter drugs may damage liver function in some cases amino-acid metabolism might have become deranged However we could find no difference at all between the patients taking these drugs and those not taking them. As mentioned already hormone-treated children and sick children have been excluded from this study

Discussion

The results of our investigation indicate a high frequency of hyperaminoaciduria (i.e. above the $m+2s$ value in normals) in mentally deficient children (Fig. 3) Nearly all cases with hyperaminoaciduria are found among the patients with cerebral lesions of prenatal origin and very often with one or more mentally retarded members in the close family Mental retardation in these cases probably depends

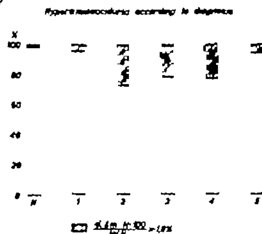


Fig 3.

on genetic disturbances. As we did not correct the values derived from morning urine samples, which were most frequent in the prenatal groups, the actual values for aminoaciduria in these groups are even somewhat higher From this study we have excluded patients with phenylketonuria in whom the diagnosis can be made more simply In cases of mild familial oligophrenia and those with cerebral damage during or after birth, aminoaciduria is normal.

In looking for patients with hyperaminoaciduria it is not necessary to examine all patients with mental deficiency but only children with prenatal lesions or malformations, especially the group of familial imbeciles and idiots. Our classification virtually eliminated the influence of environment, nutrition, age, sex, neurological abnormalities, etc. on the results.

The finding of hyperaminoaciduria points to probable metabolic disorders connected with or causing mental deficiency The number of these patients is much higher than would be expected from the rare cases with known metabolic disorders or from the studies performed with paper chromatography We hope to analyse further the patients with hyperaminoaciduria and to look for specific defects, using ion exchange column chromatography As far as we know only two investigators have also found a rather large incidence of hyperaminoaciduria in mentally deficient children [11 16]. However their classification and methods are not comparable with those of our study

Summary

Hyperaminoaciduria was found to be frequent in mentally deficient children in

an institution for mental defects. Most of the cases with hyperaminoaciduria belonged to the group with imbecility and idiocy with familial incidence of mental retardation (genetic defects). In these patients mean amino-acid excretion was significantly higher than in other patients and than normal. In the group of children with mental defects associated with multiple congenital malformations the incidence of hyperaminoaciduria is also increased. Possibly the cases with hyperaminoaciduria in this group are also caused by genetic disturbances, though familial incidence was not always found. In mild oligophrenics and children with perinatal or postnatal brain damage aminoacid excretion was within the normal range.

The index $\alpha AmN \times 100/tot.N$ was the most constant way of expressing aminoaciduria and obviated the necessity to collect 24-hr samples of urine.

This study indicates a much higher frequency of metabolic disorders in oligophrenia than the incidence of rare syndromes described up till now would suggest. The search for metabolic causes of mental deficiency can be restricted to the above-mentioned groups.

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Hypothermia Induced during Asphyxiation

Its Effects on Survival Rate, Learning and Maintenance of the Conditioned Response in Rats[1]

by BJÖRN WESTIN,[2] JAMES A. MILLER JR.,[3] and ANN BOLES

It is a well known fact that after a period of asphyxiation the human brain may be permanently damaged, even though all other bodily functions may recover completely. Therefore the ultimate test of the efficacy of any treatment for asphyxia must rest upon the degree of mental recovery as well as the success in resuscitation. Experiments have demonstrated in several species of mammals that reduction in body temperature not only postpones death from asphyxia but actually permits apparently complete recovery from exposures which are lethal for littermate controls [8, 9]. Observations on the animals which recovered in these experiments gave no evidence of residual brain damage (i.e. no behavioral defects, cerebral palsies or paralyses were seen) but no objective criteria were used to measure the degree of recovery achieved. In addition, in most of these experiments the *hypothermia* was induced *before asphyxiation* and, from the point of view of *clinical* application, tests are needed in experiments in which hypothermia is induced *during* the asphyxial period. On the other hand, 10 asphyxiated newborn infants with apneic periods up to 1 hour and 19 minutes and for whom routine resuscitative measures had been unsuccessful, have been successfully resuscitated with the aid of hypothermia. Follow up studies on these infants indicate that all are within the normal range. Subsequent studies on these infants have included physical examinations, EEG, hearing tests, psychological tests and development tests [15, 16]. However, no two of these infants had the same heredity or pre-asphyxial and post-asphyxial history. Since scientifically acceptable controls are almost impossible to achieve with clinical material, experiments were designed to test whether rats whose lives have been protected by hypothermia from a lethal exposure to asphyxia still retain their abilities to learn a conditioned response or remember a previously

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learned conditioned response. The conditioned response used in these tests was the pole-climbing avoidance response, an extremely sensitive one which has proved useful for testing drug effects [12].

Since the work of Shelley [14] shows that asphyxial survival is correlated with cardiac glycogen and that adults have a smaller supply of this metabolite than the newborn these studies on young adults constitute a more rigorous experiment than if the studies could have been performed upon newborn animals.

It is of considerable clinical and sociological importance to determine whether or not mental processes as well as lives can be protected by a given treatment for asphyxia. The experiments reported below demonstrated that if cooling was effective (to 32°C or less) neither the learning nor maintenance nor latency of a conditioned avoidance response was affected in rats which recovered from an exposure to asphyxiation which was lethal for normothermic controls This was true even though the rats were normothermic during more than one-third of the asphyxiation Less effective cooling (to minimal temperatures between 36° and 32°C) resulted in prolongation of the latency period.

Materials and Methods

Asphyxia equipment

An asphyxial chamber 11 165 7' with arm holes at each end was constructed. Three walls and the top were made of plexiglass and one side was of glass in order to permit the transmission of radiant heat from a lamp. This heat source was used to maintain body temperature during the normothermic phase of the exposure to asphyxia. At each end of the chamber was an arm hole six inches in diameter fitted with an elasticized plastic cuff to permit manipulations without introducing air during the experiment.

A gas mixture containing approximately 4% O_2, 5% CO and 91% N was used for asphyxiation. This relatively high concentration of oxygen was used because rats are so sensitive to hypoxia that almost instantaneous death occurred when mixtures containing 2% O or less were used. The gas was stored in 5 size G cylinders connected together with a common yoke in order to insure precisely the same gas mixture during the entire series of experiments. The gas source was connected t a plexiglass pipe in the ceiling of the chamber especially designed for rapid mixing of gases. The gas escaped through the floor which consisted of a 0 15 inch thick sheet of porous plastic. Because of the large size of the chamber a flow rate of 10 liters per minute was maintained during the experiments. The oxygen level was checked during each part f the experiment using a Beckman D3 Oxygen Analyzer The level held steady at 4 1 % throughout all the experiments. The time required to lower O content f the chamber to 4 1% at a flow rate f 10 liters per minute was 1 minute and 15 seconds when measured on the floor f the chamber

In the hypothermia experiments a glass jar 6 in hes in diameter and 6 inches deep, was placed inside the chamber and used for *cooling* during asphyxia. It was filled with crushed ice and water and the rats were immersed up to their necks in it. Measurements showed that the water temperature varied from 0° to 3°C

Conditioned avoidance response equipment

A plexiglass cage measuring 14 14" 14 was constructed with a sliding front panel. In the center of the cage was pole ½ inch in diameter running from floor t ceiling with rubber grippers placed around it every 2 inches. The floor of the cage was an *electric grid*, which could deliver a shock in the range of 12,000 to 18,000 volts at very low amperage. A door-bell buzzer was mounted in the cage. A transformer control

panel, and an electric timer (accuracy 0.1 second) were connected to the cage. This equipment was devised by and has been used for drug assays by Pfeiffer and Jenney [13].

The experimental animals

Unshaved male rats of the Holtzman albino strain were used as experimental animals. They were 4 weeks of age and weighed between 120–141 g. At the beginning of the experiments they were housed five animals to a cage, were fed Rockland Complete Lab Diet for Rats and were watered from bottles with tubes inserted in the stoppers. The animals were housed in the same laboratory areas as that in which the experiments were performed. The temperature of the laboratory ranged from 19° to 23°C. Rectal temperatures were taken with thermistors (Telethermometer—Yellow Springs Inst. Co.). The thermistor probe was inserted about 3 cm into the rectum and the temperature was checked before, after and on the minute during the experiment.

I. Procedure for normothermic control experiments

Fifty animals were used in these experiments to determine time of death for 37°C animals exposed to 4 per cent O_2 + 5% CO_2 – 91% N_2. The rats were tested separately and observed for collapse, first gasp, and last gasp. Immediately after the last gasp the rats were removed from the chamber and were left in the room air to determine whether spontaneous recovery could occur. No artificial respiration was employed and none of the normothermic animals recovered. During exposure to asphyxia the control rats' temperatures did not vary from the normal body temperature by more than 0.2°C.

As determined by the time of last gasp the mean survival time for the normothermic controls was 7.4 minutes. Since in the first 25 tests no animal lived longer than 8.02 minutes, this was selected as the time when the hypothermic animals were removed from the chamber. Subsequently in the second group of 25 controls one animal lived appreciably longer (8.5 minutes) and thus there is a possibility that this animal might have recovered spontaneously if removed at 8.02 minutes. Thus the exposure time for the hypothermic animals was lethal to 98% of the controls.

II. Procedure for hypothermic experiments

One hundred animals were used in the two types of the hypothermic experiments. There were 50 Maintenance animals and 50 Learning animals. The hypothermic procedure was exactly the same for both of these two groups. In each case the rats were tested separately in the chamber. Their colonic temperatures at the beginning of the experiment were between 37.0°C and 37.5°C. While normothermic they were exposed to the gas for a period of 3 minutes and then were cooled by being placed in the jar of ice water (while still in the chamber). They were removed from the chamber at 8 minutes and 1 second. The colonic temperatures were not allowed to drop below 23°C, since adult rats have difficulty in breathing even in the normal atmosphere below this temperature.

After the animals were removed from the chamber they were dried with a towel and placed on a table at room temperature to get warm and recover without assistance. Neither artificial warming nor artificial respiration was employed.

III. Procedure for teaching rats the conditioned response

The rat was put in the test cage already described. He was placed on the pole three times, viz., placed once with his head up, once with his head down, and finally was walked across the grid and allowed to climb the pole unaided. With the animals at a distance of 5 inches from the pole, the buzzer was sounded for exactly 5 seconds, after which time the shock button was pushed, once per second for three more seconds. If at any time the rat jumped onto the pole, timer, buzzer and/or shock stopped simul

taneously The animals were subjected to this procedure until they were ble to climb the pole 10 times successively

Definitions

TS – takes shock. Rat does not jump onto pole even when shocked (8 0 seconds).

UR – unconditioned avoidance response Rat jumps onto pol only after being shocked (5.1 8 0 seconds).

CR – conditioned avoidance response Rat jumps onto pole after hearing the buzzer without being shocked (0 1–5.0 seconds).

Learning – ability to learn CR. Comprised TS UR and CR in any order until and *includ ng* 10 *consecutive* CR's.

Maintenance – ability to maintain CR 24 hours after asphyxiation. This was compared with the performance of 10 tests for CR s before and after asphyxiation.

Performance – the percentage of CR s per formed during 10 consecutive tests.

Latency – length of time needed to perform the CR under standard conditions.

IV Maintenance tests

The 50 rat used in these experiments were tested for the maintenance f a conditioned response after asphyxia. The rats were subjected to a learning test 24 hours before they were to be asphyxiated in the chamber They were then exposed to Procedure II described above and 24 hours later they were again tested for maintenance of CR. The total time required to perform 10 consecutive CR s, including TS and UR's, was recorded after asphyxia. This was then compared with the time which had been recorded for the same tests before asphyxia.

V Learning tests

The 50 rats in the *Learn ng* experiments were subjected to Procedure II and 24 hours later they were taught to climb the pole. The learning ability of the *Maintenance* animals served as normal controls. Differences in the time taken to learn the conditioned response both before and after asphyxia were compared.

VI Follow up

Six days after asphyxia the animals were again subjected to the CR test. They had not been tested since their tests after asphy xia had been completed. The buzzer was sounded 10 times and the number of TS's, UR's and CR s were counted, rather than the time in seconds. This pplied t both the *Ma tenance* and *Learning* animals.

Results

Normothermic control experiments

Time of last gasps The time elapsed between onset of asphyxiation and the

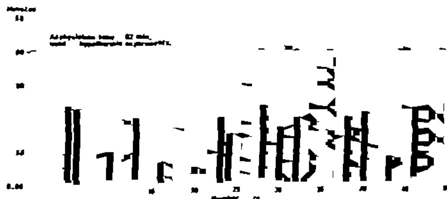


Fig. 1 The time elapsed between onset of asphyxiation (gas mixture 4 % O_2, 5 CO_2 and 91 % N_2) and the last gasp for 50 normothermic, 4-week-old rats (control series). The mean time of the last gasp was 7 40 minutes.

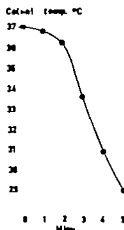


Fig. 2. Example of fall in colonic temperature during 5 minutes of cooling in ice water

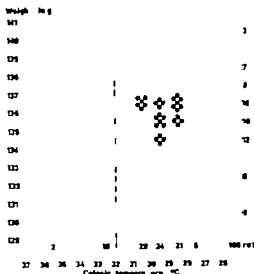


Fig. 3. Body weight in grams versus colonic temperature in C after five minutes of cooling in ice water for 100 hypothermic rats.

last gasp for 50 normothermic controls is shown in Fig. 1 The mean time of the last gasp was 7 40 minutes and only in 2 cases was the deviation from the mean as much as 15% (range 6_5-8.50 minutes)

Recovery Immediately after their last gasp the rats were removed from the chamber and were placed on a table at room temperature to determine whether spontaneous recovery was possible. None of the 50 control rats recovered. The dotted line in Fig 1 shows the asphyxiation time of 8.02 minutes used in the hypothermic experiments. As is seen in the figure only 3 rats took their final gasp after this time limit and of these gasped only 0 03 and 0 06 minutes longer Experience with a wide variety of animals has shown that under the conditions of the experiment spontaneous recovery is not possible during the last half minute of gasping Accordingly thus 8.02 minutes of exposure may be considered to have been lethal for all but, possibly one of the controls (98 %)

Hypothermic experiments

Cooling rate Fig 2 illustrates a typical example of a cooling curve This charts the fall in colonic temperature during 5 minutes of exposure to ice water in the asphyxiation chamber It shows a fall of less than 1 during the first two minutes of exposure but a precipitous fall thereafter In Fig 3 are plotted body weight and colonic temperatures after 5 minutes of cooling in ice water for 100 hypothermic rats. As is seen from the figure, the experimental points are scattered over a wide range with no definite relationship between body weight and final colonic temperature Most of the animals (78%) cooled to rectal temperatures between 25° and 31°C. Attention is also drawn to the fact that in no less than 22 animals the rectal temperatures had fallen only to the 32° to 36 C range at th end of the experiment.

Recovery In contrast to the normother

mic control rats, the hypothermic rats never reached the stage of gasping but reached at maximum, a stage of slow laboured breathing. About 7.5 minutes from the onset of asphyxiation the general condition of the animals started to im prove About 5–10 minutes after the animals were removed from the gas they had all perfectly recovered and without assistance. The righting reflex, muscle tone motor function of the legs and auro-palpebral reflex to hand clapping, all appeared normal. The immediate survival rate was thus 100 % among 100 animals. This is a significant contrast to the 50 normothermic controls where at maxi mum, 6 % (probably only 2 %) of the ani mals would have survived an asphyxia tion time of 8 02 minutes. It is emphasized once more that in spite of a rather small reduction of body temperature in no less than 22 of the hypothermic animals, they all survived. Six days after asphyxiation, all 100 rats were still alive and in appar ently good health.

Maintenance tests

Fifty animals which had recovered with the aid of cooling were tested for ability to maintain the conditioned avoidance response (CR) for a total of 48 hours (24 hours before and 24 hours following asphyxiation) Before asphyxia the rats per formed 10 CR s at a mean time of 14 0 $\pm$ 0.5 seconds. After asphyxiation the cor responding value for 10 CR s in the same rats was 14 0 $\pm$ 0.5 seconds. The difference is not significant The test results thus indicate that on an average both the performance and the latency of the CR after asphyxiation was maintained with the same accuracy and speed as before. Further analysis revealed that in nine cases the rectal temperatures of the rats had fallen only into the 36° to 35°C range during the experiment. When the latency of 10 CR s was calculated for this group of animals and compared to that of the remaining 41 rats it was found that the former group performed 10 CR s at a mean time of 17.2 seconds, while the cor responding figure for the latter group was 13.3 seconds. The difference (3 9 $\pm$ 0 7 sec onds) is significant ($P<0\ 001$) This find ing indicates that the degree of neuronal protection conferred by hypothermia is related to the degree to which cooling procedures are effective in lowering body temperature.

Learning tests

Twenty four hours after asphyxiation 50 animals which had recovered with the aid of cooling were tested for ability to learn the conditioned avoidance response The results of the learning tests of the 50 Maintenance rats before they were subjected to asphyxiation served as the nor mal control series. The mean value for the Learning animals was 47 8 $\pm$ 1 8 seconds and for the control series it was 38.6 $\pm$ 1 6 seconds. The difference 9.2 $\pm$ 2 4 seconds is significant ($P<0\ 001$) While the 50 control animals had to perform a total of 662 tests in order to learn 10 consecutive CR s, the Learning animals needed 10 % more tests for the same performance. A comparison was also made between Control and Learning animals of the percentage distribution of TS s, UR s and CR s of the learning tests rather than measuring the time needed to learn 10 CR s. It was found that no significant differences were

TABLE 1 *Percentage distribution of TS's UR's and CR's during learning of 10 consecutive conditioned avoidance reflexes*

Control = 50 untreated Maintenance rats (642 test) Learning = 50 rats Learning CR after asphyxiation (7*8 tests).

	Learning ability			
Performance	Control	Learning	Mean differences	P
TS	16.4 ± 1.5 %	21.0 ± 1.5	+ [illegible].6 ± 2.1	< 0.2
UR	5 1 ± 0.9 %	5 3 ± 0.9	+ 0.4 ± 1.3	< 0.7
CR	78.5 ± 1.6	73.5 ± 1 7	− 3.0 ± 2.3	< 0.[illegible]

present in the behaviour of the two groups during learning (Table 1) although it took the asphyxiated animals more time to perform the required 10 consecutive CR s.

The accuracy of performance was the same as for untreated controls (the 10 CR s of Maintenance animals before asphyxia) in that each of the 50 Learning animals was able to perform 10 consecutive CR s. The latency of 10 CR s was 16.2 ± 0 6 seconds for the 50 Learning animals and the corresponding figure for 50 untreated controls was 14.6 ± 0.5 seconds. The difference (1.5 ± 0 8) is probable ($P < 0\ 05$) A further analysis of the material revealed that of the 50 Learning animals, 13 had rectal temperatures between 36° and 32°C at the end of the 5 minute cooling period. A similar statistical difference was found in the time for 10 CR as noted previously The 13 animals above 32°C performed at a mean time of 18.1 seconds, while the 37 animals below 32°C took 15 6 seconds per 10 CR Together with the Maintenance animals, there wa a total of 23 whose temperatures fell only to between 36° and 32°C and 78 animals with temperatures below 32°C The mean time for 10 CR in the former group was 17 7 ± 1.[illegible] seconds and in the second it was 14 4 ± 0 4 The difference between the groups, 3.3 ± 1.3 seconds, is significant ($P < 0\ 01$) Performance and latency of CR for animals with rectal temperatures below 32°C did not differ significantly from normal controls ($P < 0\ 6$)

It was concluded that learning ability is a slightly more sensitive test than the maintenance of a conditioned response After asphyxia the time needed to learn the conditioned avoidance response wa slightly prolonged and 9 % more test per rat were needed to perform 10 consecutive CR s. However the behaviour pattern during learning and the accuracy of performance did not differ from normal controls, although latency for CR wa slightly prolonged. These findings indicate also that the degree of reduction of body temperature during asphyxiation is important. As indicated by both the maintenance and the learning tests, full protection was produced only in animals who cooled to less than 32°C in five minutes. The latency period was significantly increased for animals whose temperatures did not fall below 32°C However in the case of the animals whose colonic temperatures

TABLE 2. *Follow-up 6 days after asphyxiation*

Accuracy in performance of 10 tests per rat was determined.

Performance	50 Maintenance rats (500 tests)	50 Learning rats (500 tests)	Mean difference	P
TS	1.0 ± 0.4 %	3.4 ± 0.8 %	–.4 ± 0.9	< 0.01
UR	2.6 ± 0. %	4.6 ± 0.9 %	–0 ± 1.2	< 0.1
CR	96 4 ± 0.8 %	92.0 ± 1.3 %	4.4 ± 1.5	< 0.01

dropped to below 3?°C neither performance nor latency of CR could be distinguished from normal controls.

Follow-up tests

There were 50 animals in both the Maintenance and Learning groups. Five days after they had completed their maintenance or learning tests, the rats were put back in the grid cage and tested again, 10 times each. These data were not reported on the actual time taken to climb the pole, but rather as the number of TS's, UR s and CR s. There was a total of 500 tests for each group (Table 2)

It was found that the animals who learned to climb the pole before asphyxia retained the conditioned response 4 4 % better than those taught after asphyxia. However both groups were within the ranges of normal and the difference in performance of CR s was reasonably explained by the design of the experiments, which gave the *Maintenance* rats a total of 500 tests more than the *Learning* animals. Thus, 100 % of 100 cooled rats were able to recover from asphyxia and learn and/or maintain conditioned avoidance reflexes with an accuracy in performance of 9?–96 % six days after asphyxiation.

Discussion

Apparently the earliest recorded reference to the clinical use of hypothermia is a comment by Ibn Siena (Avicenna) [7], in which he recommended that limbs to be amputated be packed in snow and ice to lessen the pain. In 1824 Edwards observed that kittens required a longer time to drown in cold than in warm water but it was not until 1949 that the possible application of hypothermia to neonatal resuscitation was suggested [8]. Since then hundreds of experiments have established for neonatal guinea pigs, puppies, kittens and piglets that cooling is a defence against death resulting from asphyxia [9]. Hypothermia proved beneficial whether cooling was induced before asphyxiation or during asphyxiation [11].

Although the results of a clinical trial comprising 10 severely asphyxiated infants are suggestive that hypothermia is a protection against neuronal damage [16], controlled experiments were necessary before conclusions could be drawn. Rats were selected as the test animal because of their extensive use in physiological and psychological experiments particularly in conditioned response tests, their amenability and biological uniformity

The rat however is something less than

ideal for experiments whose results are to be applied to problems related to asphyxia neonatorum. The young of this species are unsuitable for these tests, since they are born in a very immature state. Because of this they are both far more tolerant of asphyxia than is the newborn human infant and are far too immature to be tested for conditioned responses. On the other hand the resistance to asphyxia of the 4-week-old rat is much less than that of the newborn human [1].

However by asphyxiating the rats in 4% O instead of 0% O_2, survival of the normothermic controls was prolonged to 7.4 minutes. This permitted a moderate degree of cooling to be achieved in the test animals which were cooled after the beginning of asphyxiation.

It is to be noted that the fully differentiated brain of the young adult is extremely sensitive to lack of oxygen and that the normothermic controls were less tolerant even of the 4% O mixture than newborn human infants are of total apnoea. Therefore the experiments reported here may be considered to constitute a more rigorous test of the effectiveness of hypothermia in protecting against brain damage than when the asphyxiated infant is cooled.

Infants dying from neonatal asphyxia have been found to exhibit cerebral edema, focal hemorrhages and neuronal damage [4]. The extent to which these changes are present in babies who recover and the extent to which they affect mental development when present is a matter of discussion.

Normothermic newborn guinea pigs who were resuscitated by means of artificial respiration exhibited changes in the brain which are similar to those observed for the human infant [7]. Many subsequently showed behavioral evidence of neuronal damage which was accompanied by distinctly impaired learning ability as compared with normal controls [3]. However none of the many cooled guinea pigs which have recovered from lethal exposures to asphyxia have shown the neurological or behavioral symptoms which Windle and Becker & Donnell [10] reported. In monkeys experimental neonatal asphyxia has been shown to produce both widespread lesions in the central nervous system and neurological aberrations [13].

In considering hypothermia as a method of resuscitation attention must be drawn to the possible drawbacks of hypothermia *per se*. Rats cooled to a temperature between 1 and 0°C showed a significant impairment in learning performance with, however the percentage of impairment decreasing as the time between cooling and testing increased. However rats whose body temperatures had not been reduced below 13.4°C performed as well as normal controls [2]. It is of interest that no ill effects from hypothermia were observed in asphyxiated human infants cooled to minimal body temperatures of 23°C [16].

Several aspects of the present experiments are of interest in connection with problems of neonatal asphyxia.

The suggestion has been made to the effect that hypothermia may merely postpone death from asphyxia without actually preventing it. In these experiments 100 young adult male rats recovered spontaneously and without observable sequela from an exposure which killed 94% of the controls and probably would have

been lethal for 98 to 100 % of the controls, had they been removed at the same time as the experimental animals. Therefore the hypothermia did prevent death from asphyxia. Similar findings have also been reported for newborn animals (guinea pigs, puppies and kittens). In every case in which this suggestion has been tested in controlled experiments it has been found not to be a valid one. Thus, the postponement of death caused by hypothermia was also accompanied by a corresponding prolongation of the time during which recovery was possible.

The most significant finding in the experiments reported here was that rats which survived a lethal exposure to asphyxia with the aid of hypothermia neither forgot their previously learned lessons nor were found to have lost their ability to learn, as indicated by a conditioned avoidance response. Thus, the hypothermia treatment not only saved their lives but to the extent that the tests were a valid measure also protected their mental capabilities. These results were not unanticipated, since no evidence of neurological sequelae had been noted in a large number of cooled guinea pigs, rabbits and puppies who had recovered from exposures which were lethal for control litter mates. The present report is important, however, because it presents quantitative data whose significance has been calculated and been found to be unequivocal.

In addition, the significance of these results is enhanced because the cooling was not begun until 3 minutes after the onset of asphyxiation. This shows that hypothermia is actually a protection against brain damage in asphyxia even though cooling is delayed until the asphyxia is well established. This finding has clinical implications, since in most clinical situations the cooling must of necessity follow rather than precede the onset of asphyxia. The experimental findings confirm the impressions gained from the first ten human infants which were cooled for asphyxia pallida in Stockholm. This impression was that the infants, whose lives we believe were saved by the treatment, were mentally and psychologically in the normal range and were continuing to show normal growth and development when last seen. These infants can be contrasted with the 19 who recovered from asphyxia pallida and were studied subsequently by Darke [5]. These children who recovered from asphyxia pallida without benefit of hypothermia were found to have a highly significant reduction in intelligence (measured by IQ) as compared with that of their nearest relatives [5].

The present study thus shows that considerable protection against asphyxia can be obtained by a slight degree of hypothermia. The favourable development of children who recovered from asphyxia by means of hypothermia is in line with the present results. Hypothermia continues to offer promise, therefore, in the future treatment of neonatal asphyxia.

Summary

The effects of hypothermia induced during asphyxia, on survival and on learning and maintenance of a conditioned avoidance response was studied in 4-week old male rats of the Holtzman albino strain.

All animals were asphyxiated in the

same gas mixture consisting of 4% O_2, 5% CO_2 and 91% N_2. The mean time of last gasp in this gas mixture determined in 50 normothermic controls, was 7 40 minutes. No normothermic animal recovered when left at room temperature to recover unaided after the final gasp.

One hundred rats were asphyxiated for 8.02 minutes. During the last 5 minutes of the exposure to the gas mixture the animals were cooled in ice water After this treatment 100% of 100 hypothermic rats recovered spontaneously

Fifty of the hypothermic rats learned a conditioned avoidance response 24 hours before asphyxiation and were tested again for performance and latency 24 hours after asphyxia. In these accuracy in performance and latency of the conditioned response were maintained.

The remaining 50 hypothermic rats were subjected to the same learning test 24 hours after asphyxiation. In these the average time to learn and the latency of the conditioned response were slightly prolonged, although the behavior pattern during the learning and the accuracy of performance did not differ from normal controls However these effects were seen only in the animals who cooled minimally during the experiment (lowest temperatures 36° to 32°C) the latency and response times of those which cooled more effectively (lowest temperatures 31 to 25°C) were indistinguishable from controls. Six days after asphyxiation all hypothermic animals maintained a normal performance of the conditioned response suggesting that the observed impairment in the learning animals was of a transient nature

The present results were discussed in relation to the problem of neonatal asphyxia.

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Lipoprotein Lipase in Plasma of the Normal Newborn

Preliminary Report

by BIRGITTA HÖGSTEDT and BERTIL LINDQUIST

In 1943 it was shown by Hahn that plasma from a previously heparinized animal contained a substance that could clear a substrate containing triglycerides *in vitro*. This substance "clearing factor" or lipoprotein lipase can be distinguished from pancreatic lipase [4]. Slack *et al.* [8] has studied the lipoprotein lipase activity in cystic fibrosis of the pancreas, a disease in which there is a now well-known failure to absorb fats due to a deficiency of pancreatic lipase. In this study measurement of plasma lipoprotein lipase activity *in vitro* failed to show a satisfactory rise following heparin administration among the fibrocystic children as compared with the normal controls. The question was raised whether this finding represented a secondary effect of poor intestinal absorption of fat with an insufficiency of the serum lipids to rise in the plasma.

It is established that the serum lipids are low at birth [6, 7]. This also applies to the triglycerides [2]. During the following weeks there is independently of the kind of fat supplied a marked rise of the serum lipids [5].

By measuring the lipoprotein lipase activity in the newborn infant immediately after birth it should be possible to study this activity in a situation before an individual has received any exogenous supply of fat or any other kind of food and when the serum lipids thus are extremely low.

The purpose of the present investigation was to study the lipoprotein lipase activity in plasma of normal newborns after administration of heparin. For comparison the same study was applied to a series of normal subjects in later childhood.

Experiments

The experimental series consisted of six full term newborn infants (Table 1). All the mothers of the children used for the investigation had had uncomplicated pregnancies and uneventful deliveries. In addition six healthy children in the ages of 7 to 17 years were studied. These studies were performed early in the morning when the children were fasting.

Method. Between 1 and 3 hours after delivery the umbilical vein was intubated by an ordinary plastic tube and a blood sample was collected with citrate to form a 10% citrate solution. Following this a 0.01% solution of heparin was injected in a dose of usually 0.1 mg/kg body weight, and blood samples were collected as before at usually three different intervals within 10 to 30 min after the heparin injection. The different blood samples were centrifugated and plasma was pipetted off.

The lipoprotein lipase activity was determined according to the method of Boberg &

TABLE 1 *Lipoprotein lipase activity in plasma of six normal newborns (Cases 1–6) and six older children (Cases 7–12) after heparin administration*

Case	Sex	Age	Weight (kg)	Elimination rat of lipoprotein lipase $T_{\frac{1}{2}}$ (min)	Extrapolated activity[a] (µEq/ml/min)	Dose of heparin (mg/kg body weight)
1	♂	At birth	2.94	18	0.0250	0 10
2	♀	At birth	3.06	12	0 0330	0 12
3	♂	At birth	3.26	17.5	0 0290	0.10
4	♀	At birth	3 63	16	0.0223	
5	♂	At birth	3.87	18	0.0293	
6	♂	At birth	4.53	12	0 0294	
7	♂	7 yrs	–5	14	0.0383	0 10
8	♂	8 yrs	20	12	0 0107	
9	♂	10 yrs	30	14	0.0480	
10	♂	13 yrs	43	12	0 0310	
11	♂	15 yrs	4 8	17	0.0393	
1	^	17 yrs	50	1	0.0250	

[a] Obtained by extrapolation of the lipoprotein lipase activity to zero time

Carlson [1].[1] The principle of the method is as follows. The substrate consisting of triglycerides, in a mixture of albumin and a buffer with incubation pH of 8.6 was incubated for different lengths of time with plasma from each blood sample, and the amount of free fatty acid split off was determined according to Dole [3]. From the values thus obtained the lipoprotein lipase activity in each blood sample expressed as microequivalents of fatty acids released per ml plasma per min, was computed. These figures were in turn plotted on a logarithmic coordinat against the time intervals for the different blood samples after the heparin injection on a Cartesian coordinate and the elimination rat of lipoprotein lipase activity was then graphically calculated Similar studies in individuals in which it has been possible to obtain mult ple blood samples after the heparin injection has shown that the decay of lipoprotein lipase act ivity from plasma, 10 min tes after a dose of 0 1 mg/kg body weight follows an exponential func tion [1]. Inspections of the semi logarithmic plots in the present investigation also demonstrated that in all patients one exponen tial adequately described the fall in lipoprotein lipase activity during the interval studied.

[1] W are grateful t Drs L. A. Carlson and J Boberg King Gustav V Research Institut Stockholm, for providing us with the method.

Results

The results are presented in Table 1

In the newborns the mean half life of the lipoprotein lipase activity in plasma was *found to be 15.4 min (range 1 –19* min) The mean value for the lipoprotein lipase activity as extrapolated to zero time amounted in the same cases to 0 031 µEq/ml/min (range 0 023–0 035) The corresponding figures for the older children investigated were 13.3 min (range 1– 1 min) and 0 034 µEq/ml/min (range 0 011 0 048)

In none of the subjects studied could any lipoprotein lipase activity be de*monstrated* in plasma before the heparin injection.

Discussion

The newborn infants investigated here probably have had low serum lipids at the time of the lipoprotein lipase study as they had not received any kind of food before this study. In spite of this the lipoprotein lipase activity in plasma following heparin administration, as judged from the values calculated at zero time, was not appreciably lower in these subjects than in the older children. Furthermore, the elimination rate of lipoprotein lipase from plasma was of about the same order in the newborns as in the older children, if any difference, the elimination seemed to be a little slower in the newborns. The findings reported here seem to indicate that in the newborn infant the production of the lipoprotein lipase enzyme need not be induced by an exogenous administration of fat or another food constituent after birth. On the other hand, it may be said that the newborn infant seems from the beginning of life to be well equipped for consuming the fat-rich breast milk, at least as far as clearing absorbed fat in the blood is concerned.

As mentioned above, in cystic fibrosis of the pancreas the lipoprotein lipase activity in plasma following heparin administration has been reported to be lower than in normal controls [8]. In the light of the results presented here this finding need not necessarily be related to the actual level of the serum lipids. Further studies into this problem are in progress.

Summary

Lipoprotein lipase in plasma after heparin administration has been studied in six newborn infants immediately after birth and in six normal children between the ages of 7 and 17 years. The activity of lipoprotein lipase was, according to the suggestions of Boberg & Carlson [1], evaluated, (1) as the elimination rate of this enzyme from plasma, expressed in terms of half life, and (2) as the value for the lipoprotein lipase activity extrapolated at zero time after the heparin injection, expressed in terms of μEq of fatty acids released from a triglyceride substrate per ml plasma per min.

The values for the lipoprotein lipase activity in plasma thus obtained were not appreciably lower in the newborns than in the older children. The elimination rate of the lipoprotein lipase activity amounted in the newborns to 15.4 min and in the older children to 13.3 min (average values); if there was any difference, the elimination of lipoprotein lipase seemed thus to be a little slower in the first mentioned group. The implication of these findings is discussed in relation to the possible role of dietary fat as inducer of the production of the lipoprotein lipase enzyme.

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Erythroblastosis Foetalis

A Survey of 491 Consecutive Cases of Rh Immunization in Pregnancy Part II Liveborn Affected by Erythroblastosis Foetalis

by ALFRED SUNDAL

In the 10-year period 1951–1961 all offspring of consecutive Rh-immunized pregnant women admitted to the Maternity Hospital in Bergen have been examined. Table 1 gives the number of stillborn and liveborn infants with haemolytic disease in this consecutive study

In a previous paper [5] findings in 31 stillborn with erythroblastosis foetalis (e.f.) have been discussed. The programme for the coming years based on the obstetrical history in previous and present pregnancy has been given, aiming at—if possible—a lower stillbirth rate and more liveborn in cases of Rh-immunization.

Table 1 gives the number of stillborn and liveborn infants with haemolytic disease It shows that 93 7 % of the offspring of Rh-immunized pregnancies were liveborn and 6.3 % stillborn.

Of 460 liveborn 1 died with haemolytic disease These cases were seen in 20 pregnancies in 10 Rh immunized women. One woman had two pregnancies resulting in stillbirths due to e.f. and one woman had twins who died. One of the infants was only mildly affected by haemolytic disease and did not need exchange transfusion, but died of cerebral haemorrhage. We thus have in our survey 20 deaths due to e.f., making 4.3 % of all the liveborn with haemolytic disease, of whom 95 7 % survived.

All the liveborn, those surviving and dying except one were transferred to the Children s Hospital for further examination and treatment as soon as possible after birth. The only case not referred to the Children s Hospital was a severely ill infant who died immediately after birth in the Maternity Hospital.

In this paper we will describe our findings in liveborn infants with haemolytic disease with regard to the obstetrical history and signs and symptoms in the newborn.

Of all the liveborn (460) 262 were given exchange transfusion according to our present indications. In 198 the haemolytic disease was so mild that no exchange transfusion was needed. We have to add four

Part I. Stillbirths Due to Erythroblastosis Foetalis published in *Acta Paediat (Stockh.), Suppl 135*: 203, 1962.

TABLE 1 *Offspring of Rh-immunized women 491 consecutive cases (1951–1961)*

			Liveborn			
Years	Stillborn	Total	Exch. transf	No treatment given	Died	Survived
1951–1954	31	82	36	46	4	78
1954–1961		378	226	152	17	361
Total						
Number	31	460	262	198	21	439
Per cent	6.3	93.7				

cases from the untreated group to the treated group as they were severely ill with e.f. at birth and died soon after birth before any treatment could be given. The number of liveborn with haemolytic disease severe enough to need treatment thus comes to 226 (58 %) The group in which the e.f. was so mild that exchange transfusion was unnecessary contains 194 cases (42 %)

In a previous study [4] of the offspring with e.f. from Rh immunized women we have discussed the cases occurring from 1951 to 1954 In this paper we will therefore include only the cases from 1954–61 comprising 378 liveborn. The cases from the last seven years have also been examined more uniformly and exactly

Indications for Treatment

When a pregnant woman with Rh-antibodies goes into labour the Maternity Hospital always informs the Children's Hospital, which admits the child immediately after birth for examination and treatment.

Our policy concerning the need for treatment in the newborn with haemolytic disease (exchange transfusions of blood) has followed these lines:

Treatment given immediately after birth. A direct Coombs positive newborn child who is severely ill with hydrops or with severe anaemia is given treatment immediately after birth (within the first 30 minutes or less) to counteract the circulatory failure and the severe anaemia.

Treatment given soon after birth The indications for exchange transfusions have been anaemia with the haemoglobin in cord blood 95 % or lower and/or 105 % or lower in capillary blood in the first hours of life (up to six hours) Or indirect serum bilirubin in cord blood 3 mg % or higher (Before September 1958 the limit was 2 mg % or higher) As a rule these children are in good health without severe anaemia and without increased venous pressure Exchange transfusions are given within the first hours after birth but not as emergency treatment.

Treatment later in the first week Exchange transfusions are then given to control hyperbilirubinaemia. Serum bilirubin values (Malloy & Evelyn's method) over a curve represented by 12 mg % at 12 hours of age 16 mg % at 24 hours of

age, 18 mg % at 36 hours of age and 20 mg % at 48 hours of age and later in the first week, have been the guide for exchange transfusions. Low haemoglobin values as mentioned above have only been the indication for exchange transfusion at birth or in the first few hours after birth.

The amount of blood for adequate exchange transfusion has as a rule averaged 160 ml/kg body weight. Exchange transfusions of blood of less than 130 ml/kg body weight have been reckoned as incomplete exchange transfusions.

As to the technique of exchange transfusions the following precautions have been taken. If the infant was severely ill with haemolytic disease (hydropic se verely anaemic, with cardiac failure) with signs such as paleness, weakness cyanosis or with respiratory distress, we have tried o lower the increased venous pressure by gradually taking more blood out than in n venous pressure of 0 mm has been btained. But we have never allowed an out deficit of more than 60 ml of blood full-term babies In severe cases with circulatory failure our object has been to ry to bring the child over the first very dangerous hours. In these cases we have intended to perform complete ex change transfusion but have been content ith an exchange transfusion of about 75 /kg body weight for the first transfu on. In such cases we have also aimed giving small out and in injections of 10–5 ml sedimented blood each time

Simple blood transfusions after the first week of life have been given in a few to correct a low haemoglobin As a for ordinary blood transfusion of 15 o a max. of 70 ml sedimented blood per kg body weight we have used haemoglobin values under 60 % in the 2nd week and under 50 after 14 days of age

A Findings in 378 Newborn with Haemolytic Disease 1954–61

Table 2 gives the *highest titre of incomplete antibody in pregnancy* in 353 patients the number of liveborn with haemolytic disease in each group the need for exchange transfusions and number of exchange transfusions given.

As highest titre of incomplete antibody in pregnancy we have registered the highest titre found on repeated serological tests for antibodies by the albumin agglutination method, indirect Coombs agglutination method and agglutination with enzyme treated cells.

The height of the titre has never been used as a guide for treating liveborn with haemolytic disease but with increasing height of incomplete antibody titre in pregnancy there is an increasing need for exchange transfusion. In the groups with the lowest titre under 1 32 61 % had no need for treatment and the 39 % needing treatment received an average of 1.3 exchange transfusions each In comparison in the group with a titre over 1 128 8 % needed treatment and each treated case received 2 0 transfusions. When th maxi mal titre of incomplete antibody 1 1024 or more (T ble 2) 20 of 41 (needed treatment, often repeat change transfusions In this grou the highest titre each treated needed n an average 2.5 exch fusions

T ble 2 also shows the t born with 4 who died I

TABLE 2 *Highest titre of incomplete antibody in pregnancy need of exchange transfusion and number of exchange transfusions given in 378 consecutive liveborn with haemolytic disease*

Highest titre of incomplete antibody	Number	Exchange transfusion		Number of exchange transfusions needed								Patients that died	
		Not given	Given	1		3	4	5	6	7	8	Not treated	Treated
< 1: 8	68	48	20	17	2	1							
1: 16	54	34	20	14	6								
1: 32	40	17	23	16	6	1						1	1
1 64	53	20	33	22	7	4						1	1
1: 128	36	12	24	12	8	3	1					1	
1 256	36	5	31	22	5	3			1				1
1 512	23	3	23	10	5	4	2	1			1	1	8
> 1:1024	41	2	39	13	14	4	4	3	1	1		1	1
Unknown	25	12	13	7	4	2							
Total	378	152	226	133	58	21	7	3	2	1	1	5	12

a titre over 1 32 and in 11 the titre was over 1 512.

The cord bilirubin was estimated in 345 newborn with haemolytic disease. The values are shown in Table 3

In 177 newborn (51 %) the cord bilirubin was under 2.9 mg % and in 168 (49 %) 3.0 mg % or higher Values over 5 mg % occurred in 63 (18 %) over 7 mg % in 28 (8 %) and over 10 mg % in 5 (1-? %) of the direct Coombs positive newborn.

As we have changed the indication for exchange transfusions because of hyperbilirubinaemia in cord blood in the period

TABLE 3 *Cord bilirubin need of exchange transfusion and number of exchange transfusions given.*

Cord bilirubin mg %	Exchange transfusion		Number	Number of exchange transfusions needed								P tients that died	
	Not given	Given		1	2	3	4	5	6	7	8	Treated	Not treated
< 0.9	10	1	11	1									
1.0–1.9	63		67	2									
2.0–2.6	51	17	68	13	4								1
2.7 2.9	7	24	31	18	5	1							
3.0–3.9	2	63	65	51	7	5						1	1
4 0–4.9	1	39	40	25	12	1			1			8	1
5.0–5.9		20	20	10	6	3	2					1	
6.0–6.9		15	15	4	7	4						2	
7.0–7.9	1	13	14		4	4		1				1	1
8.0–8.9		5	5		2	1		1	1				
9.0–9.9		4	4	1			1	1			1	1	
> 10		5	5		3		1			1			
Unknown	18	18	33	6	6	3	1					1	1
Total	152	226	378	133	56	21	7	3		1	1	12	5

TABLE 4. *Haemoglobin in the capillary blood after birth and patients treated with exchange transfusions Number of exchange transfusions given.*

Haemoglobin in the capillary blood %	Total	Exchange transfusion		Number of exchange transfusions given								Children that died	
		Not given	Given	1		3	4	5	6	7	8	Untreated group	Treated group
20– 29	1		1			1							
30– 39	2		2		1				1				
40– 49	5		5	2	2		1						2
50– 59	10	1	9	6	1	1	1					1	2
60– 69	6		6	3	2	1							1
70– 79	12		12	7	2						1		
80– 89	18		18	7	7	3		1					2
90– 99	35		35	20	9	4	1			1			
100–109	27	7	20	9	6	3	1		1			1	1
> 110	229	120	109	71	27	8	3					1	1
Unknown	33	24	9	8	1							2	1
Total	378	182	226	133	58	21	7	3	2	1	1	5	12

here studied (from over 2.7 mg % before September 1958 to over 3 0 mg % later), we shall study the 140 newborn with haemolytic disease and a cord bilirubin under 2.6 mg %. In 120 no exchange transfusion was ever needed but in 20 (14 %) we had later to perform exchange transfusions because of hyperbilirubinaemia.

Table 3 also show the cord bilirubin in the newborn who died. In only one infant was the serum bilirubin under 3 0 and this was the direct Coombs positive infant whose death was due to cerebral haemorrhage and mild e.f.

With a cord bilirubin of 3.0–6.9 mg % the average number of exchange transfusions in each patient was 1.5 compared to 3 3 exchange transfusions in each newborn when the cord bilirubin was 7 0 mg % or more

Four infants were given no treatment although the cord bilirubin was over 3.0 mg %. These patients belonged to the group of newborn with haemolytic disease who died before treatment could be given. One patient had a cord bilirubin of 3.1 mg %, he was Coombs negative on admission, but later the test turned to a weak positive there was no hyperbilirubinaemia later to indicate need for treatment.

Anaemia.—Haemoglobin values under 95 % in the cord blood or under 105 % in the capillary blood at birth have been one of our indications for exchange transfusion. Table 4 gives the haemoglobin values in 345 newborn with haemolytic disease in the first few hours after birth. In most cases it was estimated in the first 1–2 hours after birth but the age limit has been up to 6 hours of age.

As previously mentioned anaemia at birth has been one of the signs indicating need of exchange transfusion. But of 229 infants, with a haemoglobin over 110 % at birth, one or more exchange transfusions were needed in 109 (48 %) (average 1.5 exchange transfusions each) This is in

TABLE 5 *Level of haemoglobin in the capillary blood at birth in 378 cases of h d.n 1954–1961 Patients surviving and dying*

Haemoglobin %	Number	Survived		Died	
		Number	Per cent	Number	Per cent
Under 49	8	6	75	2	25
50– 79	28	21	75	7	25
80–109	80	76	95	4	5
Over 110	229	228	99 1	1	0 4
Unknown	33	30	91	3	9
Total	378	361		17	

contrast to the infants in the groups with a haemoglobin under 99 % at birth (89 newborn of whom 88 were treated) that needed 2 0 exchange transfusions each.

The degree of anaemia is proportional to the mortality from h.d. (Table 5) Thus nine died (25 %) out of 36 when the haemoglobin at birth was under 80 %—compared to one who died (0 4 %) of 228 in the non-anaemic groups (haemoglobin over 110 %) The group with unknown haemoglobin at birth includes some who died immediately after birth.

Delivery in appropriate gestational week in selected cases of Rh immunization is at present the only known method of reducing the rate of stillbirth due to e.f. Therefore it is of interest to see the numbers of spontaneous and induced labours in our series and in which gestational week the birth occurred.

Table 6 shows that in 378 pregnancies birth occurred spontaneously in 178 (47 %), after induction in 184 (48 %) and in 16 (5 %) the records were non informative There is about the same number of induced and spontaneous births. In the subgroups (births in gestational week) there is also about the same number of spontaneous and induced births. Birth in the 35th–37th gestational week thus comprises 22 (14 %) of 157 spontaneously born and 25 (14 .) of 172 in the induced group. But the death

TABLE 6 *Gestational week of spontaneous or induced labour in 378 cases of h.d.n 1954–1961*

Birth, gestational week	Number	Labour		
		Spontaneous	Induced	Unknown
35th	3	1	2	
36th	12( )	8	4(2)	
37th	32(2)	13(2)	19	
38th	61(10)	26(3)	35(7)	
39th and later	221(3)	109	112(3)	
Unknown	49	21	[illegible]	16
Total	378(17)	178(5)	184(12)	16

Number in brackets indicates newborn who died.

TABLE 7 *Spontaneous or induced labour survived and died grouped according to haemoglobin value at birth. 378 cases of h.d.n., 1954–1961*

Haemoglobin		Survived				Died		
			Labour				Labour	
	Number	Number	Spont.	Induced	Unknown	Number	Spont	Induced
Under 49	8	6	1	5			1	1
50– 79	28	21	8	12	1	7	1	6
80–109	80	76	22	4	2	4		2
Over 110	229	228	110	107	11	1		1
Unknown	33	30	23	5	2	3	1	2
Total	378	361	174	171	16	17	5	12

rate is definitely higher in the induced group (6 5 %) than in the spontaneously born children (2.8 %).

The high mortality in the induced born babies with h.d. may possibly reflect that more severe cases accumulated in this group than among the spontaneously born.

T ble 7 shows the cases grouped according to type of labour (spontaneous or induced) and the haemoglobin percentage in the newborn at birth.

Thirty-six newborn had haemoglobin under 80 % at birth. In these cases birth occurred spontaneously in nine and was induced in 17 Thus there are twice as many cases of severe anaemia in the induced group as in the spontaneous. The higher death rate in this survey in children born after induction can be explained as being due to more severe cases of haemolytic disease in this group. On the other hand the procedure of induction may also play a part in increasing the risk of fatal outcome in these severely affected babies. In all in the spontaneously born group there are 174 newborn with five deaths (2 9 %) and in the induced group 171 newborn with 12 deaths (7 %)

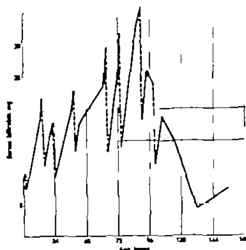


Fig 1 Eight exchange transfusions in new born with haemolytic disease This child was born in the fifth pregnancy The child mother has had the following outcome in her pregnan cies:

I 1953 Spontaneous abortion in 1st month. Abrasio.
II 1956 Livebirth at term, antibody unknown, healthy
III 1957 Livebirth, ♂. Labour induced 10 days before term. Incomplet antibody titre 1 256. Three exch. transf. Cured.
IV 1959 Livebirth at term, ♂. Titre 1 128. Two exch. transf Cured.
V 1960 Livebirth ♂. Labour induced 11 days before term. Titre 1 512. Cord bilirubin 9 0 mg %. Hgb 84 . Circulatory failure and respiratory distress. Eight exch transf. Cured (Fig 1)

TABLE 8

Number of child	Week of pregn.	Titre	Spontaneous or induced	Week of pregnancy	Date	Birth weight in g. length in cm	Age at admission	Cord bilirub. in mg	Hgb in %
I	11th 28th 47th	1:36 1:32 1:256	Spont	37th	12.-.51	2950 49	75 min	Unknown	80 cap.
II	10th 12th 20th 27th 30th 37th	1:512 1:1024 1:4096 1:1024 1:2048 1:4096	Induc.	38th	6.3.51	3500 51	40 min	Unknown	68 cord
III	40th	1:512	Spont	Term	18.-.53	4000 52	Just after birth	Unknown	4- cap.
IV	40th	1:1024	Spont.	Term	25.11.52	3430 51,5	hr	Unknown	48 cord
V	24th 28th	1:256 1:31	Induc.	38th	27.8.56	2910 4-,5	Not adm.	Unknown	Unknown
VI	24th 28th	1:4096 1:4096	Induc	38th	14.4.57	1870 47	30 min	7.0	-3 cord
VII	37th	1:512	Induc	38th	6.7.53	2260 45	3 hr	6.4	30 cord
VIIIa	34th 36th	1:16 1:256	Induc	38th	8.11.54	2400 58	3 hr	3.7	74 cap.
VIIIb	35th	1:64	Induc.	38th	11.7.58	2400 44,5	2 hr	4.4	8 cap.
IX	32nd 34th 37th	1:64 1:64 1:64	Induc	38th	4.12.58	2820 50	1 hr	4.6	43 cord
X	28th 30th	1:128 1:256	Induc.	38th	16.12.58	3070 49	45 min	4.6	8- cap.
XI	32nd 37th 39th	1:8 1:512 1:512	Induc	Term	16.12.58	3340 52	30 min	8.0	-3 cord
XII	39th	1:32	Induc.	Term	10.1.60	3060 49,5	20 min	2.4	100 cap.
XIII	28th	1:31	Spont.	38th	28.4.59	3000 50	30 min	4	80 cap.

ombs test	Age at exch. transf., hours			Age at death	Clinical diagnosis	Post mortem diagnosis	Remarks
	1st	2nd	3rd				
+ +				hr	Erythroblast. Anaemia gravis. Circ. failure.	Erythrobl. foet.	3rd pregnancy
+ +	2½	20		27 hr	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl. foet Atelect pulm.	6th pregnancy
+ +				Immediat. after birth	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl. foet. Ascites. Hydrothorax.	2nd pregnancy
+ +	3½	10½		17 hr	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl. foet.	3rd pregnancy
				45 min	Erythroblast. Hydrops cong	Erythrobl. foet. Hydrops cong (Ascites, Oedema)	2nd pregnancy Died at Maternity Hospital.
+ +				20 min	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl. foet	2nd pregnancy Died at admission.
+	4	17	43	44 hr	Erythroblast Anaemia gravis. Icterus gravis.	Erythrobl. foet.	6th pregnancy Serumbilir 15 hour after birth 19.4 mg % Sudden death at 3rd transf (Serumbilir 27.9 %)
+ +	4			6 hr	Erythroblast. Anaemia. Transf death.	Erythrobl. foet Transf death?	2rd pregnancy Cyanosis at the end of ex. tr
+ +	2½			3 hr	Erythroblast. Anaemia. Circ. failure.	Erythrobl. foet.	5th pregnancy Died during transf
+ +	1½			2½ hr	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl foet.	3rd pregnancy
+				1 hr	Erythroblast Anaemia gravis. Circ. failure.	Erythrobl. foet.	5th pregn. Severely ill. Death as transf. had just started.
+ +	1			13 hr	Erythroblast. Anaemia gravis. Circ failure	Erythrobl. foet	3rd pregnancy Severely ill from birth.
+ +				3 hr 15 min	Erythroblast. Atelect pulm. Respiratory distress.	Erythrobl. foet. Atelect pulm. H aline membr	4th pregnancy Mild f Hyaline membr Cause of death: Pulmonary atelect.
+				3 hr 15 min	Erythroblast Ascites Atelect pulm.	Erythrobl. foet Ascites. A elect. pulm	2nd pregnancy

Table 8

Number of child	Week of pregn.	Titre	Spontaneous or induced	Week of pregnancy	Date	Birth weight in g length in cm	Age at admission	Cord bilirub. mg	Hgb in %
I	11th 26th 47th	1:256 1:512 1:256	Spont.	37th	12._.51	2930 49	75 min	Unknown	80 cap.
II	10th 13th 20th 27th 30th 37th	1:51 1:1024 1:4096 1:1024 1:2048 1:4096	Induc.	38th	6.3.51	3800 51	40 min	Unknown	88 cord
III	40th	1:512	Spont.	Term	18.7.5_	4030 53	Just after birth	Unknown	4_ cap.
IV	40th	1:1024	Spont.	Term	5.11.52	3450 51,5	2 hr	Unknown	44 cord
V	36th 38th	1:_56 1:512	Induc.	38th	27.5.56	2910 4_,5	Not adm.	Unknown	Unknown
VI	36th 38th	1:4096 1:4096	Induc.	38th	14.4.57	19_0 47	30 min	7.0	_3 cord
VII	37th	1:512	Induc.	38th	6.7.55	2360 45	3 hr	6.4	30 cord
VIIIa	34th 36th	1:16 1:256	Induc.	38th	9.11.54	2400 28	2 hr	3.7	4 cap.
IIb	3_th	1:64	Induc.	39th	11._.58	2460 44,5	2 hr	4.4	6 cap.
IX	32nd 35th 37th	1:64 1:64 1:64	Induc.	38th	4.1._58	2__0 50	1 hr	4.4	45 cord
X	28th 36th	1:128 1:_56	Induc.	38th	16.1._59	3070 49	45 min	4.6	57 cap.
XI	2_nd 3_th 39th	1:8 1:512 1:51	Induc.	Term	14.1._58	3340 52	30 min	8.0	_3 cord
XII	34th	1:32	Induc.	Term	10.1.59	3060 49,5	30 min	3.4	109 cap.
XIII	38th	1:512	Spont.	38th	29.4.59	3000 50	30 min	4.7	53 cap.

Coombs' test	Age at exch. transf., hours 1st	2nd	3rd	Age at death	Clinical diagnosis	Post mortem diagnosis	Remarks
+ +	1½			14½ hr	Erythroblast. Anaemia. Atelect. pulm. Respiratory distress.	Erythrobl. foet. Atelect. pulm. Hyaline membr. Prematurity	3rd pregnancy. Severe ill from birth (sectio)
+ +	3/4			2 hr	Erythroblast. Anaemia gravis. Circ. failure.	Erythrobl. foet.	3rd pregnancy. Died at the end of the 1st transf.
+ +	3/4	14		14 hr	Erythroblast. Anaemia gravis. Circ. failure	Erythrobl. foet.	3rd pregnancy. Died just after the 2nd transf. had started.
+ +	1			13 hr	Erythroblast. Anaemia gravis. Circ. failure Resp. distress.	Erythrobl. foet. Atelect. pulm. Hyaline membr.	8th pregnancy
+				7 hr	Erythroblast. Cyanosis.	Erythrobl. foet. Cerebral haemorrhage.	4th pregnancy. Cause of death: Cerebral haemorrhage
+ +	17	21	3?½	38 hr	Erythroblast. Prematurity	Erythrobl. foet. Icterus gravis. Prematurity	8th pregnancy. Sectio, placent. praevia. Sudden death at 3rd ex. tr.
+ +	2	?0	44	45 hr	Erythroblast. Icterus gravis. Resp. distress.	Erythrobl. foet. Icterus gravis. Atelect. pulm.	3rd pregnancy. Sudden death at 3rd ex. tr. Serumbilir. 23.5 mg %

Newborn who died of Haemolytic Disease 1951–1961

As shown previously (Table 1) 20 out of 60 Coombs positive liveborn died, making a mortality rate of 4.3 %. The children who died were born between the 2nd and th pregnancy

Details concerning Rh-immunization in pregnancy birth in relation to week of pregnancy induced or spontaneous labour cord bilirubin and haemoglobin, age at death, clinical and post mortem findings and other details are given in Table 8

The last estimation of titre was performed in the 34th–35th week of pregnancy in two and between the 36th and 40th week in 18 pregnant women. Table 9 shows the height of incomplete antibody titre.

In 20 children dying of e.f. the titre in the pregnancy was over 1 64 in 19 and in 14 over 1 512. The one child with a titre of 1 32 of incomplete antibody had only mild signs of Rh immunization, and death was thought to be due mainly to the pulmonary atelectasis and hyaline membranes found at autopsy. The clinical findings were also of respiratory distress.

The serum bilirubin was estimated in the cord blood in 15 of the 21 children

TABLE 9 *Highest titre of incomplete anti body in pregnancy resulting in a livebirth with haemolytic disease and which died.*

Highest titre of incomplete anti body	Number of pregnancies
1: 3	1
1: 64	3
1 256	3
1: 512	8
1:1024	2
1:2048	1
1:4096	2
Total	20

TABLE 10 *Serum bilirubin in cord blood in Rh-immunized newborn that died*

Cord bilirubin mg %	Number
2.9	1
3–4.9	8
5–6.9	3
7–8.9	
>9 0	1
Unknown	6
Tot 1	1

(Table 10) In one the cord bilirubin was 2.5 mg % in the others over 3 0 mg %. The hyperbilirubinaemia at birth is not very marked in comparison to that in the newborn with haemolytic disease who survived.

As to the birth weight, seven out of 21 weighed under 2500 g

The haemoglobin percentage was measured at birth in 19 of the newborn, in 8 in the cord blood and in 11 (because of the cord haemoglobin had been omitted in the Maternity Hospital in these seriously ill patients) the haemoglobin in the capillary blood was estimated just after admission to the Children s Hospital (in nine in the first two hours in one at three hours of age)

Anaemia is of bad prognosis, especially when severe The haemoglobin was under 95 % in the cord blood and under 105 in the capillary blood just after birth in 18 out of 21 Two newborn without anaemia at birth had mild haemolytic disease but died of pulmonary complications and cerebral haemorrhage. Severe anaemia (haemoglobin under 60 %) occurred in 1 patients who died.

TABLE 11 *Haemoglobin in cord blood or in capillary blood in newborn dying of ha molytic disease*

Haemoglobin %	Number	Cord blood	Capillary blood	Unknown
< 30	3	3		
31– 40	1	1		
41 50	5	3	2	
51– 60	3	1	2	
61– 70				
71– 80	3		3	
81– 90	1		1	
91 100	1		1	
101 110	1		1	
>111	1		1	
Unknown				
Total	21	8	11	

TABLE 12 *Gestational week of birth and if pontaneous or nduced labour in 21 cases of h.d.n. who died (1951–1961)*

Birth, gestational week	Number of pregnancies	Labour	
		Spont.	Induced
36th	2		2
37th		—	
38th	11	3	8
39th	1		1
Term	4	2	2
	20	7	13

In one pregnancy pair of twins.

Table 1 gives the gestational week of birth and whether labour was spontane ous or induced. In 20 pregnancies resulting in 21 liveborn infants dying of haemolytic disease, labour was induced in 3 and occurred spontaneously in seven. It is noteworthy that there are more deaths in the induced groups than in the spontaneous, although there were about the same number of births in each group (Table 6) among Rh immunized women.

The age at death and the cause of death are given in Table 13. All patients who died of h.d.n. died in the first 48 hours. Thirteen died in the first 1* hours. In one case the death was caused by cerebral haemorrhage and in one atelectasis and hyaline membranes must be considered as the main cause of death.

In 19 patients the haemolytic disease has been considered the cause of death on the basis of clinical observations and post mortem findings. In 16 anaemia gravis with clinical signs of circulatory failure was the cause of death, and eight of these died in the first four hours (two also had hydrops congenitus)

In the 20 patients who died of h.d.n. all treatment was of course in vain. Many of them were already severely ill at birth, some moribund. But exchange transfu sions have been performed in apparently hopeless cases also as soon as possible after birth to give the babies their only chance of survival. Thus 16 out of 20 were given exchange transfusions. Four had no

TABLE 13 *Age at death and cause of death.*

Age at death, hours	Anaemia gravis							
	Hydrops cong.	Circulatory failure	Atelect pulm.	Transfusion death	Ict. gravis. Transf death	Atelect. and hyaline membr	Cerebr haemorr	Total
1	2	2						4
1 2		2						
2 3				1				1
3–4		2				1		3
4–6				1				1
6–12		1					1	2
12–24		2	2*					4
24–48			1		3*			4
Total	2	9	3		3	1	1	21

Also hyaline membranes.
In addition in one anaemia gra is, in one atelect. and in one prematurity

TABLE 14 *Death in connection with exchange transfusion*

Case no. (see Table 9)	Labour	Birth, gest. week	Birth weight g	Age at death hours	Hgb at birth %	Death in connection wi
VII	Induced	38th	2360	44	30	3rd ex. transf
VIIIa	Induced	38th	400	6	74	1st ex. transf
VIIIb	Induced	39th	460	3	78	1st ex. transf
XVIII	Induced	36th	1730	38	unknown	3rd ex. transf
XIX	Spont	38th	3100	45	83	3rd ex. transf

treatment three died immediately after birth one was only mildly affected but died with respiratory distress and the post mortem findings were atelectasis and hyaline membranes.

In five of the newborn death occurred in connection with the exchange transfusions. Two of them had severe anaemia and died during the first transfusion. Three had icterus gravis and died during the 3rd exchange transfusion on the second day of life.

In the patients who died in connection with exchange transfusion the cause of death was inexplicable but they were all severely ill (severe anaemia icterus gravis prematurity). These deaths account for 2.2 % of 226 patients given treatment and 1.3 % of 382 exchange transfusions.

Discussion

When Rh-immunization occurs in pregnancy we to-day face two main problems: to minimize the frequency of stillbirths, and the mortality from h.d.n. during the first days after birth. Kernicterus—once so much feared—can now be prevented provided the erythroblastotic child is admitted to a hospital with special facilities for its care during the first 24 hours of its life and provided the serum bilirubin level is kept under control by exchange transfusions of blood.

According to different statistics the overall risk of stillbirths in Rh immunized pregnancies is about 15–16 % [1 6, 7]. With adequate care the erythroblastotic newborn child has a 95 % chance of survival [2 3 7]. The perinatal mortality from e.f. is thus about 20 %. The results of the management of e f are most reliably estimated from the perinatal mortality. Stillbirths and neonatal death influence each other reciprocally. The reserved use of induction of labour and the spontaneous birth of most erythroblastotic children is supposed to give a high stillbirth rate and low neonatal death rate. On the other hand with induction of labour in selected cases at the appropriate gestational week, some that would otherwise have been candidates for stillbirth will be born alive while the liveborn group will now contain more severely ill babies, implying a risk of higher mortality. Therefore the stillbirth rate and the mortality rate must be looked upon as an entity to obtain reliable information on the management of e.f.

The stillbirth rate in this survey was 6.3 % [5]. The stillbirths were mainly cases

adequately controlled during pregnancy ith failure to predict or too late predic on of severe immunization, that were herefore admitted to the Maternity Hospital too late In the stillbirth group 29 out of 30 pregnancies (with 31 still orn infants) the foetus was already dead hen labour started In one case only was bour induced on a living child who died ust before birth.

With appropriate control in pregnancy nd reference to the Maternity Hospital due time 460 out of 491 consecutive Rh-immunized pregnancies resulted in ve births. The high live-birth rate (93 7 %) surely influenced by many factors. Most f the pregnancies resulting in live births ere adequately supervised and cases ave been referred to one particular Ma ernity Hospital in due time before birth here the experienced staff have followed e plan for induction of labour in selected ases in the appropriate gestational week.

Out of 460 erythroblastotic liveborn abies—many severely ill—20 died (4.3 %) f haemolytic disease In correlation with stillbirth rate of 6.3 % a perinatal mor lity of 10 6 % seems to be favourable

All the liveborn except one who died irectly after birth at the Maternity Hospi- al, were immediately after birth trans- rred to the adjacent well-equipped Chil- ren Hospital for supervision and care. elivery in a special unit and a short stance to transport the newborn to a ospital with special facilities is supposed be beneficial to the ill babies, who can given treatment in the first half hour ter birth.

Of the 460 liv born 262 (57 %) were ven exchange transfusions of blood ac rding to the indications given under treatment. In 198 newborn (43 %) the haemolytic disease was mild and treatment was unnecessary As four severely ill babies died before treatment could be given, 266 (58 %) of the erythroblastotic newborn were in need of treatment.

Details concerning the liveborn have been studied in 387 consecutive cases from the last seven years From the tables the findings for the highest antibody titre in pregnancy the cord bilirubin and haemo- globin can be seen in relation to the num ber of cases in each group whether ex change transfusions were necessary or un- necessary and the number of exchange transfusions given. There are correlations between severe e.f. and the necessity for repeated exchange transfusions and a high titre, high serum bilirubin, and low ha mo- globin level.

In 362 of the liveborn the baby was born spontaneously in 49 % and after induction in 51 %. One hundred and eight erythro- blastotic babies (30 %) were born between the 35th and 38th gestational week, and in this group induction of labour was per formed in 60 (56 %) and in 48 (44 %) birth occurred spontaneously

The high frequency of induction of labour resulted in a low stillbirth rate but also in some severely ill babies. The find- ings in the newborn dying of haemolytic disease are listed with special regard to the obstetrical history in previous and following pregnancies, and the severity of the haemolytic disease titre in preg nancy induced or spontaneous labour cord bilirubin and haemoglobin, age of child at death and post mortem findings. Severe anaemia at birth with circulatory failure is the greatest risk and the most common cause of death. With a haemo-

globin of under 50 % at birth two of eight newborn died and seven of 28 with a haemoglobin between 50 and 79 % also died, compared with only one out of 229 with haemoglobin over 110 % at birth.

Deaths in connection with exchange transfusions (during or immediately after) account for five newborn children. They make 2.2 % of newborn with haemolytic disease, and 1.3 % of the number of exchange transfusions given. In comparison van Praagh [3] reports the total risk of death during or soon after the exchange transfusions to be 4 % per patient and 3 % per exchange transfusion.

Walker Murray & Russell [6] point to a major difference in "induced" and "spontaneous" cases in regard to mortality from h.d.n. Five spontaneously liveborn babies survived despite severe disease in contrast five of 23 "induced" babies died. In our survey we also find a higher mortality in the induced group compared with the spontaneously born babies but the difference seems mainly to be due to accumulation of more cases of severe anaemia in the induced group.

Summary

In the 10-year period 1951–1961 the offspring of 491 consecutive Rh immunized pregnancies representative of a region of West Norway were born in one Maternity Hospital and the liveborn were cared for in one Children's Hospital. The stillbirth rate was 6.3 % and the neonatal mortality 4.3 %. The perinatal mortality is thus 10.6 %. Details concerning the stillbirths have been published in Part I [5].

All the liveborn have been studied as regards the maternal incomplete antibody titre in pregnancy, the cord bilirubin, haemoglobin at birth and need for treatment (single or multiple exchange transfusions).

A special study has been made of the newborns who died of haemolytic disease. Severe anaemia with circulatory failure was the most important cause of death. Unexplainable deaths in connection with exchange transfusion in severely ill infants with haemolytic disease also play a major role. All deaths occurred in the first 48 hours of life.

Late anaemia and the necessity for simple blood transfusions very rarely occurred. No complications with kernicterus were seen.

Adequate supervision in pregnancy, reference of selected Rh immunized women to a Maternity Hospital in due time, delivery in a special unit and immediate supervision and treatment of the affected newborn in a hospital with adequate facilities and experienced staff are of definitive importance in the management of erythroblastosis foetalis.

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TABLE 1 *G-6 P D activity in normal newborns and in idiopathic hyperbilirubinaemia.*

Newborns	No of cases with decolorization time (min) of										
	90	100	110	120	130	140	150	160	170	180	Total
Normal, non icteric		4	1	23	38						70
Neonatal jaundice, serum bilirubin of											
< 10 0 mg/100 ml			7	9	19	15	1				51
10 – 14.9 mg/100 ml		1	8	18	30	17					74
15 – 19 9 mg/100 ml	1		8	7	23	17	1	2		1	61
> 20.0 mg/100 ml			1	4	7	3	1				16

Doxiadis *et al* [6] no decolorization in 180 minutes is a sign of practically no enzyme activity and decolorization between 100 and 180 minutes a sign of partial deficiency In estimating the endpoint of the reaction a clear subjective factor appears and therefore we consider that their normal values cannot be compared with ours For that reason we have also continually assayed the activity of G-6-P D of the erythrocytes from normal, non icteric or only slightly icteric newborn infants. We have earlier presented a preliminary report on our normal values [7]

In our opinion the best description of th colour changes in the enzyme reaction has been reported by Owen [12] It is also fairly easy to estimate the time when a new colour (pink) appears. At the beginning of our experimenting with the method we used heparinized blood but no colour changes took place Later the blood was taken without added heparin and haemolyzed at once in distilled water

In 5 newborn infants decolorization was incomplete in 150 minutes Three of these infants had hyperbilirubinaemia but the neonatal period was uneventful and there were no signs of anaemia or red cell haemolysis. We are inclined to consider the four values of 160 minutes as normal. The infant with a decolorization time of 180 minutes had a maximal serum bilirubin value of 19 mg/100 ml Unfortunately the infant was discharged from the hospital before spectrophotometric determination of the activity of G-6-P D could be done Except for this infant, who might have had a partial deficiency of the enzyme it seems to us that the result of our investigation with Motulsky's test is negative

During the latter half of the investiga-

TABLE 2 *Effect of added glucose on GSH Stability Test with blood of newborns*

	No.	Concentration of GSH without incubation with APH			No of newborns with decrease of GSH concentration after incubation with APH in % of original GSH concentration			
		Mean	Median	Range	0–4.9	5–9.9	10–19 9	20–29 9
Glucose not added	53	82.9	81	5 129	41	7	5	0
Glucose added	53	84.9	80	53–123	41	6	3	0

TABLE 3 *Concentration of GSH and instability of GSH in erythrocytes of normal newborns and of newborns with idiopathic hyperbilirubinaemia*

		Concentration of GSH without incubation with APH			N of newborns with decrease of GSH concentration after incubation with APH, in % of original GSH concentration			
	N	Mean	Median	Range	0–4.9 %	5–9.9 %	10–19.9	20–29.9
Normal, non-icteric	258	79.4	76	33–155	122	61	67	
Neonatal jaundice serum bilirubin of								
< 10.0 mg/100 ml	[illegible]	81.5	82	44–128	18	3	10	1
10 – 14.9 mg/100 ml	22	79.3	79	54–115	10	6	4	
15 – 19.9 mg/100 ml	19	80.3	79	43–121	11	3	4	1
> 20.0 mg/100 ml	9	[illegible]	76	65–1[illegible]	2	4		1

tion, besides using Motulsky's test we also assayed the GSH concentration of the erythrocytes and their GSH stability.

It is considered that the erythrocytes from normal newborns have a pronounced GSH instability despite high levels of G-6-P D activity [9, 10, 17]. It has also been shown that this instability is due to a tendency towards hypoglycaemia in newborns and that this false instability disappears when a sufficient content of glucose is guaranteed during the incubation [17]. When a lack of the activity of G-6-P D exists the instability of GSH cannot be prevented by adding glucose.

In our work the erythrocytes from the first 53 children were investigated with Beutler's GSH Stability Test both with and without added glucose. No essential difference between the tests with and without added glucose could be demonstrated (Table). Three of the 53 infants, however, had a somewhat decreased stability of GSH when glucose was not added, but none of them had a decrease over 20 % of the original concentration of GSH.

Naylor and co-workers [11] consider a fall of 50 % in GSH concentration after incubation with APH as a positive GSH Stability Test. Zinkham [17] characterizes persons with a concentration of GSH under 20 mg/100 ml erythrocytes as "reactors".

In Table 3 the concentrations of GSH in normal and jaundiced infants are presented. For the different groups the mean values, the median values, the ranges and the percental decrease in concentration after incubation with APH are reported.

Like other investigators we have found a great range. On the whole our mean values coincide with the investigations mentioned before. There is no essential difference between the large group of normal newborns and the groups of infants with varying jaundice.

None of the children with severe jaundice has had a concentration of GSH below 50 mg/100 ml erythrocytes. Neither the icteric newborns nor the normal ones had a decrease of the concentration of GSH above 30 %.

In these cases, apparently other mechanisms than a defective activity of G-6-P D must be the cause of the jaundice.

Summary

Between March 1961 and March 1962 the activity of G-6-P D of the erythrocytes from normal and jaundiced new borns was assayed with the aid of a semi-quantitative screen test. During the latter half of the investigation, Beutler s GSH Stability Test was also used. The material consisted of normal non icteric newborns and of newborns with varying degrees of hyperbilirubinaemia of unknown aetiology Sixteen out of these had maximal serum bilirubin values of 20 mg/100 ml or more and 62 had serum bilirubin values between 15 and 20 mg/100 ml. No certain case with deficient G-6-P D activity in the erythrocytes has been found.

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Basophil Leucocytes and Heparinoid Substances in Diabetes Mellitus

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The basophil leucocytes in the blood have received increasing attention since the elaboration by Moore & James [33] of a simple method for counting these cells. It has thus been shown that the basophil leucocytes are under the influence of hormones; that they decrease in number on administration of cortisone [7 13] or of corticotrophin [7 35]; that the number of these cells is reduced in hyperthyroidism [7 10 12 26]; and that it varies with the phases of the menstrual cycle and during pregnancy [7 11].

It is of interest to note that the tissue mast cells react to the above-mentioned hormones in the same way as the basophil leucocytes [7 46].

A question that has been the subject of much discussion in recent years is also whether any relationship exists between tissue mast cells and basophil leucocytes. Both stain metachromatically. It has been demonstrated that mast cells contain heparin or heparin-like substances [28] and histamine, [41]. Graham *et al.* [22] showed that the basophil leucocytes are carriers of histamine an observation since confirmed by Code & Mitchell [14] and others. Much evidence is also available that the basophil leucocytes contain heparin or heparin-like substances [30, 31 37 38, 47]. Another observation suggesting some relationship between these two types of cells is that in some animals, such as the rabbit the number of basophil leucocytes in the blood is high, while the number of tissue mast cells is relatively low. In the rat however the ratio is the reverse. In 1960 Asboe-Hansen [5] described a case of urticaria pigmentosa with generalized tissue mastocytosis and a co-existent increase in the number of basophil leucocytes.

The aforementioned findings indicate an intimate functional relationship between tissue mast cells and basophil leucocytes. Boseila [7] concluded that basophil leucocytes are probably the circulating members of the mast system, representing a mobile, easily available and transportable source of acid mucopolysaccharide and histamine.

Hellström & Holmgren [24] showed that the number of tissue mast cells decreases with age and that in females, 0–39 years old, the number of these cells is invariably higher than in males, but the same in both sexes above this age limit. Jones *et al.* [27] reported that the concentration of Sf 12–20 lipoproteins is lowest in females below 50 years, which would imply a low so-called atherogenic lipoprotein content. This lipoprotein content increases with age, and in ages above 50 years its concentration is the same in both sexes. There is thus a certain inverse relationship between the number of mast cells and the atherogenic lipoprotein content.

In 1952 Nikkila & Majanen [34] found the protamine-binding effect of the blood in atherosclerotic patients to be reduced. They ascribed this reduction mainly to a decrease in the amount of heparinoid substances in the blood. Engelberg [16] reported that a low heparin content of the blood was significantly correlated with an increased amount of Sf 0–12 lipoproteins. A similar co-varia

TABLE I *Survey of material*

Number of cases	♂	♀	Age (years)	Duration of diabetes (years) Recent	1–4	5–9	10–14	15–19	20–24
60	29	31	1½–23	14	13	8	16		
Number of cases of diab. *angiopathy*					—	*1*	*11*	*1*	*1*

tion though not significant was found between the heparin content of the blood and Sf 12–400 lipoproteins. In late vascular complications in diabetes mellitus the Sf 12–20 lipoproteins are clearly increased [15]. In analogy with what was said above this would imply a low heparin content

The purpose of the present investigation was to elucidate problems bearing on diabetic angiopathy Several authors have drawn attention to the high frequency of atherosclerosis in diabetics while most are of the opinion that those forms of atherosclerosis-like changes occurring in diabetes are manifestations of a specific diabetic angiopathy It was thought that investigation of the basophil white blood cells and heparinoid substances in diabetics with without late diabetic complications might contribute to the elucidation of vascular lesions in late diabetic complications To our knowledge no such investigation has hitherto been performed.

Material

As a control group we used 44 children (30 boys and 14 girls) aged 3 months to 15½ years (average 8.4 years), who had been admitted to the Department of Paediatrics in Lund for evaluation of educational maturity or because of enuresis or for social reasons. The ESR was normal in all of them, and none of them showed evidence of active infection at the time of sampling. In 15 of these children the heparinoid substances in the blood were also *studied*.

The material consisted of 60 diabetic patients, 29 boys and 31 girls, aged 1 year 8 months to 23 years (average 12 years). Most—44—had been treated at the Department of Pediatrics, Lund on one or more occasions in 1959 1960 or 1961 The remaining 16 were examined at the outpatient department. Nearly all of them had been under our (G.E.) observation since the onset of the disease. Of the 60 patients, diabetes had been recently diagnosed in 14 while the remaining 46 had been known to have diabetes for 1 to 22 years with an average of 7 7 years (Table I) Fourteen of the patients showed evidence of late vascular complications in the form of retinopathy and/or diabetic nephropathy It is clear from Table I that 11 of these patients had had diabetes for 10–14 years, while the remaining three had had the disease for 9 16 and 2. years, respectively One patient an 18-year-old girl, who had had the disease for 13 years died. She had severe vascular changes (Kimmelstiel Wilson syndrome) and died of uraemia with terminal pericarditis and colitis.

All the patients had been treated by dietary measures and insulin. A minor number of the patients had also received oral treatment with tolbutamide and/or DBI preparations.

It should be pointed out that all the patients—except the one in the above mentioned fatal case—were in a good general condition. None of them showed evidence of acute infection at the time of the examination. Some of the patients with recent diabetic onset were examined during the

cut phase but all of them were followed up and samples were collected also after stabilization of the disease

Methods

The number of *basophil leucocytes* was determined by the method of Moore & James [33] as modified by Rorsman [4].

All samples were collected between 8 a.m. and 1 noon, and all of them were collected by one of us (T.L.) who also counted the blood cells (double test). A volume of 25 mm capillary blood was mixed with 215 mm of the following solutions:

0.29 ml $M/15$ Na_2HPO_4
0.71 ml $M/15$ KH_2PO_4
5.0 ml isotonic saline
5.0 ml 0.1% toluidine blue (Merck)
5.0 ml absolute alcohol

Haemolysis was secured by addition of 10 mm fresh filtered solution of 10% saponin (Riedel-de Haë) in 20% ethyl alcohol. Fuchs-Rosenthal's counting chamber was filled and allowed to stand for 10 minutes in a moist chamber in order to give the leucocytes time to sediment. The metachromatically stained basophil leucocytes were then counted, and the number in a chamber was multiplied by 3.125, which gave the number of basophil leucocytes per mm³

The *heparinoid substances* in the blood were determined by the protamine titration method of Allen *et al.* [1]. This method was chosen because it lends itself well to clinical use

Samples were collected in the morning before breakfast. A solution of protamine sulphate (kept in the refrigerator at about +4°C for 1 to 7 days) containing 1 mg per ml was added in increasing amounts to 10 glass test tubes. To tube I was added 0.02 ml (0.02 mg), to tube II 0.04 ml ... to tube X 0.2 ml (0.2 mg). Blood obtained by careful venipuncture was blown down to a graduated tube containing 1.0 mg (0.1 ml) heparin, until the tube was filled to the 11 ml mark. After the heparin and the blood had been properly mixed, 1 ml of the blood heparin mixture was transferred by means of a pipette to each of the 10 tubes, which were then vigorously shaken. The tubes were allowed to stand for 1 hour at room temperature after which the result was read, i.e. lowest concentration of protamine sulphate in which a clot formed

In 28 patients the specimens were titrated with both protamine and polybrene. Polybrene, a synthetic polymerized quaternary ammonium salt, has recently been introduced as a new heparin neutralizing substance [*9 40 45 48]. Polybrene is said to be superior to protamine. It is more stable, less sensitive to extraneous factors and recommended particularly for revealing even minute amounts of heparin by titration [20, 1]. Since the heparin binding effect is also stronger the following titration series was set up: Tube I 0.01 ml (0.01 mg); tube II 0.02 ml etc. to 0.11 ml (0.11 mg). The procedure was otherwise the same as for protamine titration. The results obtained with protamine and polybrene are compared below

	Protamine			
Polybrene	0.12 mg	0.14	0.16	0.18
0.07 mg	1			
0.08	7	1		
0.09		14		
0.10		2	1	
0.11			2	

Neutralization of blood to which had been added 0.1 mg heparin requires, for example, 0.14 mg of protamine sulphate, but only 0.09 mg of polybrene. This result is in agreement with the findings of Godal [20] and Keat *et al.* [29].

Protein-bound hexoses, which are often increased in diabetic angiopathy, were determined in 26 cases with the anthrone method of von Holt [25]. The normal range for this method is 120–145 mg/100 ml.

Blood sugar (capillary blood) was determined by the method of Hagedorn-Jensen

TABLE 2 *Basophil leucocytes in controls and patients*

	Number	Age (years)	Basophil leucocytes/mm³ mean and range
Controls	44	8.4	39.0 (12–78)
Recent diabetes mellitus	14	6.0	37.0 (12–62)
Diabetes mellitus, duration 1 25 years	46	14.2	35.5 (0–81)
Diabetes mellitus, duration (years)			
1–4	18		32.8 (0–51)
5–9	8		35.5 (9–62)
10–14	16		33._ (0–81)
15–19	2		28.0 (12, 46)
20–24			25.0 (19 31)
Diabetes mellitus without lat complications	32		31 4 (0–62)
Diabetes mellitus with late complications	14		34.1 (1 –81)

Results

Basophil leucocytes

The mean number of basophil leucocytes in the control group was 39 0 per mm³ (range 12–78 per mm³) This normal value agrees with that found by earlier authors.

Thus, Moore & James [33] reported a mean value of 46.7/mm (range 11–107) for 36 adult males and of 40 6/mm (range 8–68) for 33 adult females. Boseila [7] gave a value of 28.3/mm for 170 healthy adults, while Rorsman [42] found a mean of 44.8/mm Mitchell [32], who studied the basophil leucocytes in 67 healthy children, aged 6 months to 12 years, gave a normal value of 45.0/mm (range 13–84). Braunsteiner *et al.* [9] reported a normal value of 28.03/mm for 56 persons. As in previous investigations [7 32], no correlation could be found between the number of basophil leucocytes and age or sex On the other hand Mitchell [31] found that the number varied substantially during the first 6 weeks of lif Boseila [7] studied the diurnal variation and found that the number tended to rise during the afternoon hours.

Table 2 and Fig. 1 show no difference between the number of basophil leucocytes in the normals and diabetics. It is of interest to note that the group with late complications did not differ in this respect from that without complications (Table 2 and Fig. 2)

In two patients repeated examinations failed to reveal any basophil leucocytes at all. One of these patients was a 14-year old girl, with uncomplicated diabetes, which had been diagnosed at the age of 1 year She had been cared for on three occasions between 1959–1960 at the Paediatric Department and during none of those spells in hospital could any basophil leucocytes be demonstrated. The other patient was an 11 year-old girl who had had diabetes mellitus for 1 year It is known that the number of basophil leucocytes is reduced in some diseases, such as urticaria [43 44] hyperthyroidism [10, 36] and the acute stage of infectious diseases [32]. The above-mentioned 14 year-old

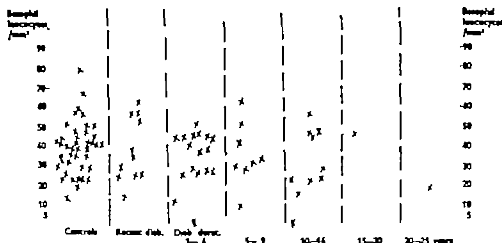


Fig 1. Basophil leucocytes in controls and in material.

girl showed no evidence of such conditions, but it should be mentioned that her diabetes was difficult to control. The other girl, however had her first attack of urticaria barely one month after

No correlation could be found between the basophil leucocytes, on the one hand, and the blood sugar cholesterol or protein bound hexoses, on the other

The course of the basophil leucocytes was studied in six newly diagnosed cases

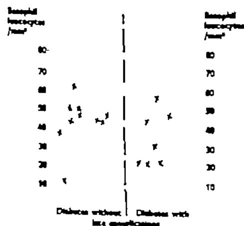


Fig. 2. Basophil leucocytes in diabetes with and without late vascular complications.

of diabetes. In three cases the number was reduced (9 6, and 12/mm³) on the first day Two of them had received insulin before sampling In two patients the number of basophil leucocytes was high (63 and 75/mm³) before insulin was administered. In the sixth case the number of basophil leucocytes was 37/mm Common to all of these cases was the fact that the number of leucocytes became stable at normal level (between 35 and 55/mm³) one day to one week after admission and institution of therapy

Heparinoid substances (Table 3)

Three subjects in the control group showed coagulation in the tube containing 0 12 mg protamine Allen *et al* [1] claim that coagulation normally occurs at 0 14 mg or more. In 20 of *4 nomals in Nikkilä & Majanen series [34] it occurred at 0 16 mg and in the remaining four t 0 14 mg but their subjects were adults while the above-mentioned three controls were 8–11 years old Titration with polybrene gave the same results.

TABLE 3 *Heparinoid substances in blood in controls and in patients*

	Number	0.12 mg	0.14 mg	0.16 mg	0.18 mg
Controls	13	3 (20 %)	8		2
Diabetes mellitus, recent	8	1 (12.5 %)	4		1
Diabetes mellitus, duration (years)					
1–4	9	(22.2 %)	5	1	
5–9	7	(28.5 %)	5	—	—
10–14	1	4 (33.3 %)	5	1	2
15–19	3	—		—	—
20–24	2	(100 %)	—	—	—
Diabetes mellitus without lat complications	29	6 (20.7 %)	18	4	3
Diabetes mellitus with lat complications	11	5 (45.5 %)	4	1	1

It is clear from Table 3 that no substantial difference occurred until the patients had had diabetes for 10 years. One-third of these patients then showed a titre of 0 12 mg A clear difference was found between uncomplicated diabetes and diabetes with late vascular complications: 45.5 % in the latter group had a titre of 0 12 mg against 20 7 % in the former group i e a decreased content of "heparinoids" in long term diabetes.

No correlation was demonstrable between the amount of heparinoid substances in the blood and the number of basophil leucocytes (Fig 3)

The heparinoid substances and the protein bound hexoses are listed in Table 4 from which it is clear that the higher the protein bound hexose content the more protamine was necessary to produce coagulation A similar correlation was not found between heparinoid substances and cholesterol.

TABLE 4 *Heparinoid substances in blood in relation to protein-bound hexoses and cholesterol*

	Number of cases	Heparinoid substances in blood			
		0.12 mg	0.14 mg	0.16 mg	0.18 mg
Protein bound hexoses/blood (mg/100 ml)					
100–150	8	4	3	1	—
150–175	5	1	4	—	—
175–200	3	—	3	—	—
200–225	3	—	1	1	1
225–250	1	—	—	—	1
Cholesterol/blood (mg/100 ml)					
100–150	1	—	1	—	—
150–200	4	3	1	—	—
200–250	8		6	1	—
250–300		1	1	—	—

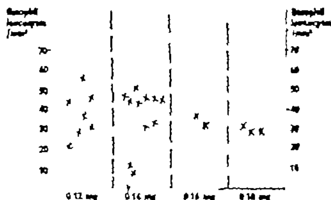


Fig. 3. Relationship between basophil leucocytes and heparinoid substances in the blood

Discussion

During the last decade a number of investigations have been published on the relationship between heparinoid substances and atherosclerosis.

Nikkilä & Majanen [34] assessed the heparinoid substances in the blood by protamine titration in 2 patients with atherosclerosis. They found the blood protamine binding effect in these patients to be weaker than in 24 age-matched normals. They ascribed this partly to reduction in the amount of heparinoid substances in the blood and pointed out that this might be of significance in the pathogenesis of atherosclerosis. This view was shared by Antonini [4], who found a clear reduction in the heparinoid substances in the blood in atherosclerosis as well as very high beta/alpha lipoprotein quotient. Engelberg [16] found, as mentioned above, an inverse relationship between heparin in the blood and Sf 0–400 lipoproteins, a ratio that was significant for the Sf 0–12 lipoproteins. He measured the heparin content of the blood by an cetylamine method devised previously by him and his co-workers [19]. Pescador et al. [38], who studied heparin in the blood, cholesterol and plasma proteins in general atherosclerosis, found the plasma heparin values to be reduced, and they stressed that hypoheparinaemia is a basic humoral feature of atherosclerosis. In 1958 Yamagi et al. [49] published a paper on the blood heparin level and serum lipoproteins in 108 schizophrenics. They found a significant negative correlation between the Sf 0–20 lipoproteins and the blood heparin and between the cholesterol and blood heparin. A number of papers have been published on the value of heparin in the treatment of atherosclerosis and some of the authors reported heparin to have a favourable effect on late vascular complications in diabetes. Engelberg et al. [15] found markedly high values for the Sf 12–20 lipoproteins in 17 patients with diabetic glomerulosclerosis. Heparin was given in three cases with consequent reduction of the Sf 12–20 lipoprotein content and clinical improvement. Finley et al. [18] gave a preliminary report in which 10 cases of diabetic retinopathy responded to heparin therapy.

The present investigation shows that the heparinoid substances in the blood are decreased in the presence of late diabetic complications. It should be mentioned that in the presence of such late complications the blood contains a larger amount of protein bound sugars [17]. Table 4 shows that the higher the protein-bound hexose content, the larger is the amount of prota

mine necessary to produce coagulation. This agrees well with the assumption of Nikkilä & Majanen [34] that an increase of the mucoproteins is also accompanied by an increase of the protamine titre values. Greenspan [23] pointed out that the mucoproteins are always increased when the protamine titre is high, but no *significant correlation could be demonstrated.* Consequently if a specific heparin determination method is used the blood heparin values obtained would be low in the presence of late diabetic complications. It is clear from Table 3 that in one patient with complications coagulation did not occur in the test tubes containing less than 0.18 mg. This patient died one week later with grave vascular changes and uraemia. Her protein bound hexose content was markedly increased (140 mg/100 ml). The number of basophil leucocytes was within the normal range.

Engelberg [18, 19] reported that protamine titration is an unreliable method and non specific for heparin. Allen *et al.* [1] mention that although it may not necessarily be a test for heparin, it is a measure of a coagulation defect resembling that produced on intravenous administration of heparin. Nikkilä & Majanen [34] also pointed out that the method is indirect and non-specific. Only part of the protamine binding effect is due to heparin-like substances, but they expressed the view that this part is sufficient to influence the protamine titer.

No correlation could be found between the number of basophil leucocytes and the amount of heparinoid substances in the blood. The patient in whom no basophil leucocytes could be demonstrated had normal protamine titres. Angeli *et al.* [*] found no correlation between the number of basophil leucocytes and the heparin activity in the plasma in normal or pathological serum. On injection of heparin into man Angeli *et al.* [3] found an increase of the basophil leucocytes after 2 hours. Piette & Piette [39] reported a decrease on injection of heparin into the rabbit and Bosella [8] found a significant reduction of the basophil leucocytes on injection of heparin into the rabbit, while protamine produced no change. The last mentioned author expressed the view that the reaction observed reflects a general systemic reaction to heparin. Braunsteiner *et al.* [9] found no change after a single injection, but they noted a significant reduction in the fourth to tenth day when depotheparin was given daily.

Braunsteiner *et al.* [9] also studied the basophil leucocytes in diabetes mellitus, hyperthyroidism, myxoedema and lipoid nephrosis, for example. They found a slight but significant increase in 90 adult diabetics who were not in a state of stress (mean 41.6/mm³—normal value 28.0 mm³). Nothing is said as to whether late complications were present or not. The authors thought that in disturbed fat metabolism the basophilia might be a reaction to increase the release of heparin. This hypothesis would according to them explain the change in the number of basophil leucocytes in thyroid disease and lipoid nephrosis, where the values are high. But they found no change in the level after fat loading and no correlation between cholesterol and basophil leucocytes, i.e. the same as in the present investigation.

The present investigation does not support the findings of Braunsteiner *et al.* [9]. If anything a tendency was found for the basophil leucocytes to be reduced in number in juvenile diabetes mellitus. As to

e number of basophil leucocytes in re diabetes, the results obtained were ɩt uniform. Three patients showed low alues initially but two had high initial alues. In fresh cases, however there are y factors which may influence the umber of basophil leucocytes. Further ions are necessary to elucidate ome of these factors. It is also planned to udy the reaction of the basophil leucocytes to the administration of insulin.

Summary

The present investigation showed a re uction in the content of heparinoid substances in the blood in the late vascular complications of diabetes. This finding suggests the occurrence in diabetic angiopathy of a disorder pathogenetically similar to that in atherosclerosis. The decrease found in the amount of heparinoid substances in the blood cannot be explained by a change in the number of basophil leucocytes, which are normal in diabetes mellitus. The number of cases, however is not large and further investigations are in progress

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Prognosis after Puberty for 442 Asthmatic Children Examined and Treated on Specific Allergologic Principles

by E. RYSSING and E. WINGE FLENSBORG

The object of the present study has been to throw light on the postpubertal prognosis for a group of asthmatic children examined and treated systematically for a long period on the principles stated below.

Diagnosis and Treatment

The principles of examination and treatment at the clinic are shown in Table I.

After the usual recording of the past history and a physical examination, the patient is submitted to radiography of the lungs and paranasal sinuses, otologic examination, and measurements of haemoglobin and blood sedimentation rate. Further leucocyte and differential counts are performed, as well as count of eosinophils in the blood.

The allergologic diagnosing comprises skin tests in the forms of scratch test and subsequent provocation trials [9] with the allergens which have given positive skin reactions. Using the inhalant allergens, we employ either sniff test or inhalation test, or both, and in some cases, natural exposure trials. During the treatment renewed skin testing and, if desired, provocation trials are performed. The treatment consists primarily in elimination, to the greatest possible extent, of the releasing allergens from the patient surroundings. At the same time hyposensitization is started, but only with the allergens that have provoked positive reactions in provocation and/or exposure trials. A few of the patients have, however, been treated with allergen extract without preceding provocation trial, either because it has been impossible to carry these out owing to persistent symptoms, or because the patients have been too young. In very rare cases extract of house dust or feathers has been given solely because the children have not improved in response to previous treatment. The hyposensitization is started and continued ambulantly in the clinic—at first three times weekly and later at longer intervals, from 1 to 4 weeks. If the patient's condition permits, the treatment is usually continued during stays in hospital and sanatorium. We have used only Danish allergen extracts.

The children in whom no specific allergy has been demonstrated have been treated with a Danish bacterial vaccine [3].

The main principle regarding the duration of treatment with extract and vaccine has been that of treating the patients until symptom free for one year. None have received prolonged steroid therapy.

Starting Material

The starting material comprises all the asthmatic children submitted to out-patient treatment in the clinic who had completed their 15th year at the time of investigation in 1960 ... total of 503 patients.

The patients received questionnaires containing ... number of questions to be answered in order to elucidate the course of illness after the treatment within the period following the latest consultation. Incompletely answered questionnaires were in several cases

TABLE 1 *Diagnosis and treatment*

Diagnosis	Treatment
History	Elimination of allergens in question
Skin-testing (scratch)	Hyposensitization
Provocati testa	Bacterial vaccine (Da ish stock accine)
Nasal test (snuff)	Prolonged change of en ironment
Inhalation test	Possible hange of li ing quarters
N tural exposure	
Peroral pro ocative test with food	

supp lemented by telephoned or personal i q iiry

Table 2 shows that we succeeded in procuring information on 98.4 of the patients. The ight for which no or insufficient data were available comprised one oligophrenic and one schizophrenic patient a well a one settled in Nairobi and two l ing in Canada. One refused to answer the quest tionnaire while in two cases the diagnosis w doubtful

Two men had died—one from lymphogranulomatosis and the other by drowning Thus, none had lied from asthma.

F fty-one of the patient have not been treated in the linic the majority because they lid not want treatment Very few patients ha not been treated because they had experienced no more than a single ttack prior to thei reference F nally some ha e left Copenhagen This group will not be further described being among other things too small to act a control group.

TABLE 2 *Follow up of 503 asthmatic children at 1 years of age or later*

Result of inquiry			
Inquiry answered			
Treated t linic	442	495	(98.4%)
U treated	51		
Dead (not of asthma)	2		
Inquiry not nswered		8	
Total		503	

The analysed series

The analysed series thus consisted f 442 treated asthmatic children of whom 28 were boys and 153 girls.

Table 3 shows the age distribution at the onset of the disease The lisease here means asthma or asthmatic bronchitis. It is seen that in 6 of the cases the disease had started before the age of 5 years. Thi per centage i a little l wer than those in most other series reported, which range between 73 and 8

The patient were next lassified according to the severity of the disease prior to the treatment We employed Kraepelien s classification [1] (Table 4) The first group, containing the mildest cases, consisted of chil dren with less than f ve periods of illness a

TABLE 3 *The age distribution at the onset of asthma*

Age at onset of asthma (years)	Number of children (boys nd girls)		
0–	88	296	(6)
1	111		
2– 4	97		
5– 6	46		
7– 9	54		
10–14	37		
Uncertain	9		
Total	44		

TABLE 4 *The classification of the patients according to the severity of asthma prior to the treatment.*

Group	Number of asthmatic periods per year	Number of children	[illegible]
I	< 3	[illegible]	[illegible]
II	5–10	115	[illegible]
III	> 10	1[illegible]7	42
Uncertain		41	9
Total		443	

year The next group, that f moderately severe cases, comprised the children with from five to ten periods f illness a year To the severest group belonged the children with more than ten periods f illness a year as well as the children having almost conti nuous asthmatic symptoms. W see in Table 4 that the series is burdened with relatively many severe cases.

In spit f intensive control and contact we did not succeed in carrying through hyposensitization and vaccine therapy of all the patients until these had been symptom-free for a whole year Forty per cent discontinued the treatment themselves, while in 16% the treatment ceased owing t change f address or for other reasons.

Forty-eight per cent have had one stay or more in health resorts f not less than 3 months duration, either in Norway or at suitable places in Denmark. Sixteen per cent moved *during the period of treatment* and 33% after it

Results

At the follow up the patients were classified in three groups on the basis of th data procured. (1) The absolut ly symptom free i.e. the patients who had been symptom free for the past year or longer (2) The patients with occasional dyspnoea of a non-asthmatic character and pos-

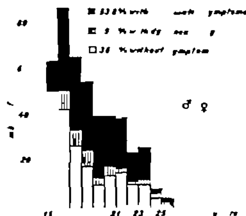


Fig 1 Distribution of the patients according to age and at tus t follow-up.

asthmatic symptoms—either intermittent mild wheezing typical asthmatic attacks, or continuous symptoms

Otherwise no assessment has been at tempted of improvement or exacerbation by comparing the condition before and after the treatment as such an assessment would be very uncertain on the basis of the material in hand.

Fig. 1 illustrates the patients ages at

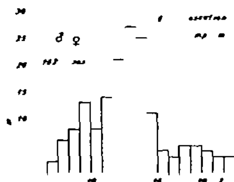


Fig 2. This figure illustrates the ages t which the 162 symptom-free children were free of their disease A marked accumulation is seen within

TABLE 5 *The relation between the age at onset of asthma and the chance of obtaining freedom from symptoms*

A shown in T ble 6 the great majority of the hildren with early onset of asthma were submitted ery late to treatment. Thus, thi group i not representati of asthmatic hildren with an early onset of the disease

Age t onset of asthma (years)	Number of hildren	Symptom free for the past year or longer: Number	
0– 1	88	27	30.7
1 2	111	25	22.4
3– 4	97	35	36 0
5–15	137	60	43.7
Uncertain	9	3	
Tot l	44	16_	

their disease A marked accumulation is seen within the years of puberty

Next we aimed at investigating the influence of various factors on the course

The data set out in Table 5 suggest that the prognosis is worst when the disease comes on early in childhood. However this impression is hardly correct.

Table 6 shows that the great majority of the children with an early onset of the disease were submitted very late to treatment These children were the first to be referred to the clinic after its establishment in 1940 and they were in fact referred because they continued to be ill. Thus, this group is not representative of asthmatic children with an early onset of the disease

The late reference to the clinic is illustrated graphically for the whole series in Fig 3. It is seen that 164 (37) children first attended for treatment after not less than 5 years of illness and 71 (16 .) after at least 10 years of illness. The late institution of treatment in 54 . of the cases must necessarily have influenced the results

the follow-up They were now all between 15 and 25 It is seen in the chart that only 30 8 had been quite symptom-free for the past year and that 0 4 % had experienced occa ional dyspnoea and in some cases coughing while 53 8 . had asthmatic symptoms. These three groups were approximatel evenly distributed in the itted age-classes

Fig 2 illustrates the ages at which the 102 symptom free children had got rid of

Table 7 shows that there is a greater chance of obtaining freedom from symptoms if the treatment is instituted early

TABLE 6 *The age distribution according t onset of asthma and start of treatment*

The great majority of the hildren with early onset of asthma were submitted very lat t treatment.

Age t onset of asthma (year)	Number of children	Number of years bet een onset of sthma and st rt of treatment (of children): 0–2	3–4	5–9	10–15
0– 1	88	0	8	47 7	44.3
1	111	7._	18	51 4	23.4
3– 4	97	4.9	18.8	40.4	6._
5–15	137	63.7	19 7	14 6	0

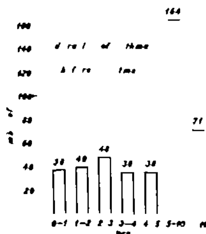


Fig. 2. This figure illustrates the late reference to the clinic for the whole series. It is seen that 37 % of the children first attended for treatment after not less than 5 years of illness, and 16 % after at least 10 years of illness.

46 % having become symptom free in response to treatment started within 4 years of illness, against 29 % in response to treatment commenced after 8 years of illness.

The severity of the disease prior to the treatment was also found to influence the prognosis. In Table 8 the series under review has been divided according to severity before the treatment in the above mentioned groups. Group I comprises children with less than five periods of illness a year. Group II, those with five to

TABLE 7 *The relation between the duration of asthma before treatment and the chance of obtaining freedom from symptoms*

Duration of asthma before treatment (years)	Number of children	Symptom-free at follow-up %
0– 3	163	46.0
4– 7	125	31.5
8–13	13	[illegible]

ten periods a year and Group III, those with at least ten periods of asthma a year or almost continuous symptoms.

We see that 49.5 % of the patients with mild asthma had become symptom free against only 27.8 % of those with severe asthma before the treatment.

As illustrated in Table 9 the patients with a familial predisposition to atopic illness have a smaller chance of becoming symptom free only 33.4 % of the children with a hereditary predisposition having become symptom free against 41.8 % of those without.

Table 10 shows that presence of other atopic illnesses in asthmatic children gives a lower percentage of symptom free, the percentage figures being 32.6 and 45.7 for patients with and without other atopic illnesses respectively.

TABLE 8 *The relation between the severity of asthma before treatment and the status at follow-up*

Severity of asthma before treatment Group	Number of children	Status at follow-up: Symptom free	Dyspnoea only	Asthma	Uncertain
I	[illegible]	49.5	7.0	39.4 %	4.1
II	115	37.4 %	12.2	48.6	1.7

TABLE 9 *The relation between a familial predisposition to atopic disease and the status at follow up*

Predisposition to atopic disease	Number of children	Status at follow-up: Symptom-free	Dyspnoea only	Asthma
No	148	41.8 %	9.4 %	48.8 %
Yes	276	33.4 %	10.[illegible]	56.5 %
Uncertain	18	8 children	0	10 children
Total	442			

TABLE 10 *The relation between the presence of other atopic disease and the status at follow-up*

Other atopic disease	Number of children	Status at follow-up: Symptom-free	Dyspnoea only	Asthma
N	138	45.7 %	11.6	4[illegible].7 %
Yes	304	32.6	8.6	58.8
Total	442			

TABLE 11 *The relation between the number of manifest allergies and the status at follow-up*

Number of manifest allergies	Number of children	Status at follow-up: Symptom free	Dyspnoea only	Asthma
0	150	46.7	10.7	4[illegible].7
1	109	30.4	12.8	47.7
2	120	32.5	6.7	60.8
3	53	18.9	7.5	72.6
4–5	10	0	0	100
Total	442			

Finally the prognosis depends in a marked degree on the number of manifest allergies.

We see in Table 11 that the percentage of symptom free patients decreases with increasing numbers of manifest allergies. Of the patients negative to skin test 40.7 % were found to be symptom free at the follow up. Of the patients with one manifest allergy 30.4 % were symptom free; of those with two manifest allergies 32.5 %, of those with three manifest allergies 18.9 %, while none of the patients with four or five manifest allergies were symptom-free.

Table 12 records the prognosis for asthmatic patients with complicating manifest pollen and/or mold fungus allergy

TABLE 12 *The relation between a complicating manifest pollen and/or mold fungus allergy and the status at follow up*

Manifest allergy to	Number of children	Status at follow-up		
		Symptom free	Dyspnoea only	Asthma
Pollen	30	4	0	26
Mold fungus	12	1	0	11
Pollen + mold fungus	3	0	0	3

The prognosis is very bad for such patients Only four out of 30 children with complicating pollen allergy became quite symptom free and only one out of 12 with complicating mold fungus allergy Three patients with complicating pollen plus mold fungus allergy still had symptoms at the follow up.

Discussion

The result is depressing in so far as no more than 37 % of the patients have been quite symptom-free for one year or more, despite careful examination, control un specific and specific treatment—often for several years. Further the obtained freedom from symptoms was doubtless in an unknown proportion of the cases attributable to puberty and hardly to the treatment.

A proper evaluation of the effect of the treatment requires, however a matched control series which does not exist Our knowledge concerning the spontaneous course of asthma in children is scant and fragmentary A small number of minor series have been reported in the literature in which the percentages who became symptom free at the age of puberty ranged between 30 and 64 % [4 5 11].

In Flensborg's [7] series, comprising 293 asthmatic children, 131 were over 18 years of age at the follow up Of these 41 % had no attacks and 22 % were quite symptom free. On renewed analysis of this series in 1957 when all the patients were over 18 years old Ryssing [8] found that only 28 % were quite symptom free

Of Rackemann & Edwards [6] 449 asthmatic children, of whom an unknown number had been given a short-term and not further elucidated specific treatment, 30 % were symptom-free 20 years later

Thus, no particular effect of the treatment has been demonstrable in the form of an increased percentage of symptom free patients.

The fairly poor result may to some extent be due to the relatively many severe cases in the series, as well as to the fact that a very large proportion of the children were first submitted to treatment from 5 to 15 years after the onset of the disease These children are therefore likely to have had chroni pulmonary changes at the start of the treatment. Further the treatment was interrupted in 56 % before the patients had been symptom free for more than one year It must be added however that many of these hildren had been under treatment for a long period, often several years

It is surprising that the treatment has not had a greater effect, as we know that specific hyposensitization against a few inhalant allergens is capable of changing a manifest allergy into a latent allergy [10].

The effect of the treatment cannot of course be evaluated solely on the basis of the percentage obtained of symptom free patients. However, we did not feel justified in assessing the rate of improvement from the information obtained, but 90.3 % of the patients declared themselves improved.

A final evaluation of specific allergologic treatment of asthma in childhood will probably require prolonged experiments of treatment using the double-blind technique.

Summary

By means of questionnaires and/or personal inquiry information has been procured on the 603 asthmatic patients seen in the Clinic who were over 15 years of age in 1960. Useful data were obtained for 98.4 % of the series under review.

Four hundred and forty two of these patients had been treated in the clinic on the lines stated. At the follow up 30.8 % had been quite symptom free the past year or more. Nine point four per cent had occasionally experienced dyspnoea and some of these also a cough, while 53.8 % continued to have asthmatic symptoms. None had died from asthma.

The fairly poor result was due partly to the relatively great number of severe cases (4 %) in the series, and partly to the fact that far too many had not been submitted to treatment till after a long period of illness: 37 % after not less than 5 years of illness and 10 % after at least 10 years of illness. It is shown that the chance of obtaining freedom from symptoms is greatest for the patients submitted to early treatment.

The prognosis is moreover poorest in cases of severe asthma and a familial predisposition to atopic illness; further in cases with other associated atopic illness and with increasing numbers of manifest allergies, as well as in cases with complicating pollen and/or mold fungus allergy.

Finally, a markedly increased tendency towards freedom from symptoms has been demonstrated during the years of puberty.

A final evaluation of specific allergologic treatment of asthma in childhood will probably require prolonged experiments of treatment using the double-blind technique.

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Congenital Choanal Atresia

Report of a Clinical Series with Special References to Early Symptoms and Therapy

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Congenital atresia of the choanae, which form the communication between the nose and the pharynx, is an uncommon though not extremely rare anomaly. The first clinically diagnosed and treated case of choanal atresia was reported by Emmert in 1853 [8]. A classic description of bilateral choanal atresia was given by Ronaldson in 1880 [17]. In 1945 Durward *et al.* [7] compiled some 400 cases in a report containing 300 references. Although in the last 10–15 years choanal atresia has received increasing attention, the nasal passages of newborns are not routinely examined and unless marked symptoms of respiratory obstruction are present, early diagnosis of atresia may well be overlooked.

Choanal atresia may be associated with other congenital anomalies such as the tetralogy of Fallot [6], defect of the intraventricular septum, or patent ductus arteriosus [11]. In one reported case it coexisted with the Treacher–Collins syndrome [14]. In the presence of these probably more conspicuous anomalies, atresia may go undetected, even when it constitutes an important factor in the symptomatology.

Choanal atresia may be either unilateral or bilateral and either osseous or membranous. The obstruction may be complete or it may be only partial, in which case there will be a small central perforation.

The ratio of bilateral to unilateral cases varies in different series. Affection of the right side is, in unilateral atresia, reportedly more common than that of the left. The condition is said to occur more often in girls than in boys. A hereditary tendency is considered by some authors to be implicated [9, 10].

Choanal atresia has little effect on the normal development of the paranasal sinuses and the nasopharynx. The ciliary activity of the nasal mucosa is not affected, and with the establishment of nasopharyngeal patency the sense of smell is completely restored. It is remarkable how rarely choanal atresia is complicated by paranasal sinusitis or by otitis. Usually the hearing is quite normal.

Choanal atresia is an embryonic maldevelopment of unknown cause. The nasal

vity is of ectodermal origin and develops from olfactory fossae which gradually deepen to form a sac, separated from the primitive pharynx by an epithelial plate of mesodermal origin, the oronasal membrane. When, in the seventh week of embryonic life, this membrane ruptures, each nasal cavity communicates with the primitive pharynx via a primitive choana. Choanal atresia is thought to occur when the membrane, instead of rupturing, undergoes organization during the development of the nasal cavity and septum [2]. According to other theories the anomaly is due to proliferation from the fetal environment of the choanae. An exhaustive account of the various theories has been given by Poch-Viñals & Ramos Calvo [15].

For an appreciation of the grave consequences that choanal atresia may entail, it is necessary to consider certain physiological facts.

The human nose is primarily a respiratory organ. Nasal breathing is a normal and natural reflex in the newborn infant as well as in the adult while mouth breathing is a voluntary act seldom practised before the age of five months [3]. Newborns rarely breathe through the mouth and at least three weeks are needed to teach them to do so when required.

Aversion to mouth breathing is based on the congenital impulse to draw the air towards the olfactory organ in the nose from which it proceeds at a gradually increasing rate into the nasopharynx. This process presupposes firstly a free passage through the nose and choanae but it is also essential that the nostrils be smaller in diameter than the choanae. This difference in the size of the nasal orifices and the choanae is a factor which affects the resistance in the nose and, consequently the intrathoracic pressure [13, 16].

When the choanae are obstructed the newborn does not open its mouth to inhale. On the contrary, the lips are pressed more tightly together, the nasal alae are dilated and the auxiliary respiratory muscles are brought into action. Unless the infant cries, however, or sucks in its lips so far that they become separated, inspiration will not take place and the infant will die of suffocation. If at autopsy the nasal passage is not closely examined, the diagnosis will be atelectasis.

Symptoms and Diagnosis

I. *Complete bilateral choanal atresia*

This condition constitutes an immediate threat to the life of a newborn. The symptoms are:

1. Periodic attacks of anoxia to the point of asphyxia.

2. Severe dyspnoea in connection with sucking.

3. Thick gelatinous mucus in the nasal cavities.

If the infant survives the neonatal period, the most characteristic symptom will be a constant nasal discharge which increases when the infant inclines its head forward. In addition to this there will be continuous mouth breathing, anosmia and closed nasalization, all of these symptoms persisting in adulthood. Complications may also arise from the paranasal sinuses or the ears, but are as mentioned previously quite rare.

Diagnosis. 1. The symptomatology is typical and should be so well-known that the presence of choanal atresia is immediately suspected.

2. The nasal passage can readily be tested by inflating one cavity at a time

with a Politzer bag The resistance encountered will also indicate whether the obstruction i partial or total [1]

3 A soft rubber catheter is inserted in th nose in the presence of atresia it will be arrested at the level of the choanae 30–3° mm from the nostril and will not be visible in the pharynx

4 A dye e g fluorescein for ophthalmic use can be in tilled into the nostril one drop at a time When atresia is present the dye will not as in normal conditions be observable on the posterior pharyngeal wall

5 Roentgen examination with instillation of contrast medium should be conducted in all cases where choanal atresia is suspected The secretion must first be aspirated out and the mucous membrane constricted A lateral view will show lodgement of the contrast medium against a backward and upward sloping septum at the level of or a few millimeters anterior to the junction between the hard and soft palate

6 In exceptional cases examination with a metal probe as suggested by Beinfield [3 4] may be advisable Arrest of the probe at a distance of less than 32 mm from the nostril will point to atresia If it is possible to advance the probe more than 44 mm total atresia may be ruled out The examination is not entirely free of risk.

II *Partial bilateral choanal atresia*

The symptoms characteristic of this form of atresia are largely similar to those attending complete obstruction though they are less pronounced. At times the diagnosis may be overlooked, since at roentgen examination the contrast medium may seep through into the pharynx

III *Complete unilateral choanal atresia*

The clinical picture is seldom as dramatic as that in bilateral atresia Occasionally however the normal side may be blocked by pressure against the pillow or mattress or may become filled with secretion. The resulting symptoms will, especially in infants under five months, be just as severe as in bilateral atresia.

Diagnosis Con tant unilateral nasal obstruction, thick secretion in the nasal cavity and unilateral excoriation of the nostril are suggestive of choanal atresia Unilateral choanal atresia may be detected by a simple procedure which should be part of the routine examination of dyspnoeic newborns. First one then the other nostril is occluded. Pronounced difficulty in breathing through one nostril should lead to the suspicion of choanal atresia on the unoccluded side A necessary condition is that the infant does not cry during the investigation for then it will inhale through the mouth. The diagnosis may be subsequently verified by the examinations described under bilateral choanal atresia

IV *Partial unilateral choanal atresia*

This is an uncommon form which is difficult to diagnose since occlusion of the normal side will not necessarily cause dyspnoea. If all the relevant tests are carried out however a comparison of the different findings should serve to establish the diagnosis.

Treatment

The aim of all forms of treatment is, of course complete restoration of the normal nasal passage Except in rare cases such

storation should not and cannot be ef eted during the neonatal period, here it primarily a matter of saving the infant om acute asphyxia.

The nasal cavity of a newborn is so nall as to greatly impede operative mea ures for eradication of atresia The opera- on must be performed by the transnasal ute and the risk of injuring the base of e skull or the spinal canal between the las and epistropheus is appreciable nce the distance between the choanae d these vital structures is barely 12 mm].

A more conservative treatment during e neonatal period will likewise be in cated by the presence of associated con nital anomalies, e.g heart disease pre aturity poor general condition, or un rnourishment.

Treatment of bilateral choanal atresia in wborns

As in all treatment of the air passages, e most important consideration is main nance of a free airway Since the infant es not open its mouth to breathe the ly feasible measure is insertion of a aryngeal tube Tracheotomy is seldom quired and should be avoided. Initially e infant will have to be fed through a be In about four weeks it will have arnt to breathe through its mouth and eding will gradually become easier reast feeding usually fails, however

A simple and ingenious method of solving problem both of breathing and feeding recently been described by McGovern "] An ordinary nipple is fastened by ans of a tape around the ears. At the tip the nipple are one large or two small eral perforations which ensure the infant adequat air supply Feeding is done by filling and refilling the nipple with milk. The infant sucks on the nipple obtaining ir alternately with milk via the perforations.

If satisfactory breathing is not established and feeding presents great difficulties, the advisability of an early operation for choanal tresia must be taken into consideration. Generally a Lichwitz trocar is used. It is advanced along the floor of the nose until it meets the tresic wall. The latter is then pierced with the needle—sometimes offering considerable resistance since the atresia is usually osseous. The perforation is enlarged and a polyethylene t be is inserted. The method is not entirely satisfactory since the opening readily becomes reoccluded by granulations on removal of the tube

Beinfield [4] has described a procedure whereby the pharyngeal mucosa on the posterior aspect of the atresia is used to cover the bony surfaces. The nasal mucosa on the anterior aspect and the bony tresia are removed with a Lempert curett The above-mentioned pharyngeal mucosa is kept intact and is retracted for removal of the osseous septum. With a scalpel a star-shaped incision is made in the remaining membrane on the floor of the nose With the aid of a catheter a polyethylene tube is introduced into the nose retrogradely via the pharynx. The membrane will thus cover the exposed bony surfaces against which it is pressed and will come into contact with the nasal mucosa. The polyethylene tube should be about 4_ mm long and its diameter should coincide with that of the anterior nares. The tube is retained for not less than four weeks.

Beinfield recommends the performance of this operation within 24–48 hours after birth It is not without certain hazards, but the use of a metal shield in the epipharynx should lessen the risks [5]. Experience of this operative method is still very limited.

II *Treatment of unilateral choanal atresia newborns*

These cases do not present such diffi cult problems during the neonatal period. Th obstructed side should be cleared by

suction from time to time and the nasal opening on the affected side protected with ointment

III. *Treatment at a later stage*

The nature of the symptoms must determine the time for final corrective treatment of the choanal atresia. As a rule an operation for either bilateral or unilateral atresia should be performed before the child reaches school age. The operation is the same for both forms and follows in general one of two methods: the transnasal or the transpalatine.

The transnasal approach is employed when the obstruction is entirely membranous—an uncommon form—and also when the palatal arch is very high. A poor general condition also may necessitate the use of this procedure. When the nasal cavities are especially wide and permit good visualization, the transnasal approach may be the method of choice. Beinfield's method merits trial in such cases. By fracturing the inferior concha and displacing it upwards a good view of the atresic region may be obtained.

The transpalatine method of operating on choanal atresia has major advantages. Here direct visualization of the atresic area facilitates adequate surgery.

Due to the smallness of the reported series, except for that collected by Durward *et al.* [7], it has not been possible to formulate any definite conclusions respecting early symptoms and treatment.

Our own Series of Choanal Atresia

An account of our series referable to the period 1941–1961 may therefore be of value. During this period 29 cases of congenital choanal atresia were treated at the Otolaryngology Department of Karolinska Sjukhuset. Table 1 shows the distribution with respect to sex and the type of atresia.

TABLE 1

	Bilateral	Unilateral *Right*	Unilateral *Left*
Boys	5	4	3
Girls	9	6	2
Total	14	10	5

The series thus comprises 14 cases of bilateral and 15 of unilateral atresia. Of the latter patients twice as many were affected on the right side as on the left. Seventeen of the patients were girls and 12 were boys.

Tables 2 and 3 *show the distribution of* complete and partial atresia, and also of osseous and membranous forms.

There was only one case of bilateral and no case of unilateral partial atresia.

No familial disposition emerged from the histories. This of course does not rule out the possibility of undiagnosed cases in sibs.

As regards complications referable to the paranasal sinuses and the ears, two patients had had unilateral sinusitis, in each case on the non-atresic side. Six patients had had otitis—two at the age of 2 years, one at 5 years, and three as adults. In one of the adult cases, however, the choanal atresia was associated with meloschisis, and in one case a dry central, clinically asymptomatic perforation was present.

Of the 29 patients, one boy had congenital mitral stenosis, and one woman

TABLE 2.

	Bilateral				
	Complet both sides	One side partial Right	Left	Both sides partial	Total
Osseous	4	2	0	0	6
Membranous	2	1	0	1	4
Osseous + membranous	4	0	0	0	4
Total	10	3	0	1	14

d pronounced left-sided meloschisis. In ese cases choanal atresia was not dia osed until the ages of 1 and 24 years spectively

Table 4 shows when the diagnoses were tablished.

Thus, eight cases of bilateral choanal resia were not diagnosed during the onatal period, two of them were cases of tal osseous atresia Of the unilateral ses, which were invariably total 13 were t diagnosed during the neonatal period

Table 5 shows the age at onset of mptoms.

From a comparison of Tables 4 and 5 it apparent that although symptoms p-ared during the first week in 17 cases, e diagnosis was established during this riod in only eight cases. Nine of the tients had symptoms for more than ten years before choanal atresia was dia gnosed.

Among symptoms manifest as early as the first week cyanosis during feeding was dominant. It occurred in nine cases all bilateral. Since the other five patients with bilateral atresia sought medical advice only as adults their case histories are based largely on their own statements

Other common symptoms were pronounced nasal obstruction and continuous nasal discharge Many of the patients had long histories and only in three cases two bilateral and one unilateral did the onset occur after the age of one year

Twenty-six of the 29 patients treated at the E.N.T Department have been operated on. The other three are not yet four years of age and are being kept under observation with a view to future surgery

TABLE 3

	Unilateral				
	Complet Right	Left	Partial Right	Left	Total
Osseous	7	5	0	0	12
Membranous	1	0	0	0	1
Osseous + membranous	2	0	0	0	2
Total	10	5	0	0	15

Table 4

Diagnosis established	Bilateral	Unilateral	Total
1st week	6	2	8
1st year		1	3
Later	8	1	18
Total	14	15	29

Table 5

Age at onset of symptoms	Bilateral	Unilateral	Total
0–1 week	9	8	17
Up t 1 year	2	6	8
Over 1 year		1	1
Total	14	15	29

Five illustrative cases of choanal atresia three bilateral and two unilateral are presented here

Case 1

Girl, born Sept 27 1961 No hereditary data of interest. Delivery normal. Within 4 hours after birth the infant was observed to become cyanotic when it attempted to suck. A catheter test indicated choanal atresia, and roentgen examination showed complete bilateral atresia. For the first 14 days an indwelling pharyngeal tube ensured satisfactory breathing subsequently the infant was able to breathe spontaneously through its mouth. It was tube fed during the first 14 days, after which it gradually learned to ingest food in the normal way

Comment In this case the first symptoms were noted in connection with attempts to suck The diagnosis was made immediately and a pharyngeal tube was inserted. After 14 days the infant had already learned to breathe through its mouth.

Case 2

Girl, born Sept 23 1952 No hereditary data of interest Delivery normal The child was not asphyctic at birth but cyanotic attacks occurred about half an hour later Oxygen was administered to the stomach. An hour or so later there was repeated hematemesis, possibly due to the oxygen administration. Following insertion of a pharyngeal tube approximately 2 hours after birth an appreciable improvement occurred An attempt to pass tube through the nose disclosed an obstruction. At roentgen examination the contrast medium did not pass from the nose into the nasopharynx. Tongue, pharynx larynx trachea and esophagus were normal, but the infant could not breathe without the pharyngeal tube Despite the use of specially designed tubes pressure necrosis were after some weeks, detected in the pharynx Since in addition, the pharyngeal tube interfered with tube feeding, tracheotomy was performed after six weeks. The tracheostoma was retained until the child was three years old The patient was hospitalized for 1½ years. At the age of one year certain abnormalities were noted, oxycephaly and large protuberant ears. The intelligence however showed a largely normal development At age seven, transpalatine choanal plastic reconstruction was performed and the presence of total bilateral bony choanal atresia was established.

Comment This case which dates back nine years, illustrates the diagnostic difficulties that may be encountered in bilateral choanal atresia. Insertion of a pharyngeal tube was life-saving procedure carried out before the diagnosis had been established Owing to complications of intubation tracheotomy was essential despite the difficulties associated with maintenance of a tracheostoma.

Case 3

Girl, born Sept 1_, 1939 No hereditary data of interest Delivery normal. Patient had left-sided facial cleft. As from 1938 she underwent extensive reconstructive surgery for this anomaly After the cleft had been completely closed she had pronounced nasal obstruction and a continuous discharge of thick secretion. When examined at the

..N T Department, bilateral choanal trecia was found and roentgen examination showed t be total. The patient was subjected to eral transpalatine choanal plastic reconuction.

Comment. The total bilateral choanal atre- a in this case was not detected until the patient was 22 years old. Only when her symptoms were aggravated following plastic reconstruction of the meloschisis did he symptoms of an associated anomaly be- ome apparent

Case 4

Boy born March 10, 1952. Delivery nor nal. No hereditary data of interest. During first day in the maternity ward a con- tinuous, thick discharge from the right nostril was observed. There was no difficulty in sucking The patient was referred to a con ltant otologist, who diagnosed choanal tresia of the right side Roentgenograms ed total atresia. At age 1½ years the had otitis following an upper ·spiratory t infection, and t age 3 he had left illary sinusitis. At six years of age he nderwent transpalatine plastic reconstruc- on of the choana, and total osseous tresia the right sid was found.

Comment. In this case of complete unila eral osseous atresia the diagnosis was esta blished within 24 hours. The patient had y slight symptoms until he was operated at the age of six.

ase 5

Girl, born Feb. 25, 1951. Delivery normal.) hereditary data of interest. The mother served, within the first few days, a dis- harge from the right nostril. N difficulties ere experienced in sucking. Throughout arly childhood, the patient woke up repeat dly every night with severe dyspnoea. Medi- al advice was frequently sought and the ymptoms were ttributed t bronchial sthma. The constant nasal discharge and octurnal dyspnoea led to nervousness and bilitation The correct diagnosis was not established, however unt l the child was eight years old, when roentgen examination dis- closed total atresia on the right ide At ope ration via the transpalatine approach, a to- tal osseous obstruction of the right choana was found. After the operation both nasal breathing and leep became normal. The girl s general condition improved rapidly

Comment. This case of complet unilateral osseous atresia was regarded as bronchial asthma because of the nocturnal dyspnea Despite treatment the symptoms persisted until the diagnosis of choanal atresia was established. After adequat treatment the child became entirely healthy

Conclus ons

Although choanal atresia is not a com mon disease it should be kept in mind when acute attacks of cyanosis occur im mediately after birth. Two cases demon strate the way in which simple procedures may serve to avert the life-endangering hazards associated with complete bilateral choanal atresia A pharyngeal tube almost always suffices to ensure satisfactory breathing Tracheotomy should be avoi- ded since a tracheostomia in newborns invariably entails great difficulties. \ a rule the infant cannot be suckled but requires tube feeding After some week when the infant has learnt mouth breath ing it can be spoon fed.

In unilateral cases the initial sympt m are much milder and the diagnosis n y therefore be overlooked.

Case 5 exemplifies the misinterpretation of typical symptoms as bronchial asthm Case 4 demonstrates that even in unilat ral cases the diagnosis can be established within the first ..4 hours on susple n of atresia

All of the patients, including those wi- bilateral atresia did well and none wer

adversely affected by deferment of operation until the most expedient time

Only in three of the 40 patients operated on at the E.N.T. Department was transnasal perforation performed before the age of 1½ years. Fifteen patients, including these three cases, were operated on via the transnasal and 11 via the transpalatine route. The latter approach has been used routinely since 1951. With this procedure the drainage tube in the nose must be retained for at least 2 months. A prefitted supporting plate sutured to the palatal flap expedites healing. When after some days the plate is removed the incision along the dental arch will be practically healed.

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CASE REPORT

The Syndrome of Familial Atrial Septal Defect Heart Arrhythmia and Hand Malformation (Holt Oram) in Mother and Son

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Holt & Oram have recently reported a syndrome of atrial septal defect (ASD) and congenital anomaly of the hands, observed in four generations of a family [4]. Some of the patients also exhibited a tendency to an unusual type of cardiac arrhythmia. McKusick, who noted this syndrome in a mother and daughter has suggested the name "atrio-digital dysplasia" [5]. The present report describes the occurrence of the condition in a mother and son, both of whom have been successfully operated upon for the ASD. These patients have been previously referred to in connection with cytogenetic studies in congenital heart malformations [1].

Case 1

M.H a woman born in 1929, suffered during childhood from lability to respiratory tract infections but had no symptoms suggestive of streptococcal infection or rheumatic fever. She also tired easily on exertion and had attacks of palpitation at rest. She has had three children, born in 1949 1951 and 1957. These were all born about one month before term and their birth weights were 2350, 2530 and 2930 g, respectively. Between the births of her second and third children there were two pregnancies which resulted in abortions. Sterilization was performed in 1957 because the patient had, for a couple of years, been suffering from increasing dyspnoea on exertion and a tendency to ankle edema. In October 1961 she was not able to walk upstairs more than one floor without a pause and, even at rest, she experienced episodes of precordial oppression and pain, which radiated into the left arm. Her dyspnoea was never accompanied by cyanosis.

A heart murmur and cardiac enlargement were detected in 1946. In 1960 she was examined, together with her son (see below), at the pediatric clinic. Apart from somewhat slender body build her general condition was not suggestive of heart disease. Her hands, however, were found to be malformed (Fig. 1). The thumb was absent on the right side and on the left hand, it was replaced by a small radial finger with three phalanges. This abnormal digit showed ulnar deviation of its distal phalanx and was situated in the same plane as the other fingers. *Heart.* Inspection, palpation and auscultation of the precordium revealed pronounced arrhythmia. A rather weak and soft pulmonary

[1] At the time when this report was compiled, the author was a trainee sponsored by the National Institutes of Health, United States Public Health Service training program at the Institute for Medical Genetics (Director: Prof. A. Böök).

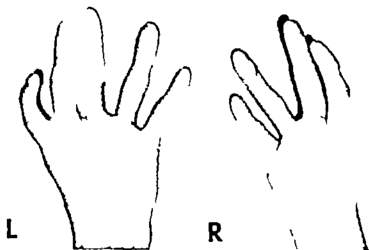


Fig 1 The hands of the mother (Case 1). The types of thumb anomalies in this case have both been described in two families with the Holt–Oram syndrome reported previously

ejection murmur of low frequency was heard and recorded, and the second sound over the upper left sternal border was broadly split 0.05 sec without accentuation.

ECG recorded on this occasion (Fig 2, 1960) showed marked arrhythmia of a peculiar type. For short periods sinus bradycardia was observed with a frequency of 40–50 beats per minute and slightly varying configuration of the P waves. AV conduction time during these periods was 0.20–0.26 sec. At times no unequivocal P waves were seen for several seconds, and then an ectopic supraventricular focus was activated resulting in ordinary ventricular complexes but no P waves. Sometimes one or perhaps several such ectopic foci gave rise to a burst of 7 beats with a rate of 100–150 per minute, an irregular rhythm and slight to moderate aberrance of the ventricular complexes. During periods of slow ectopic rhythm, ordinary P waves were sometimes seen to occur immediately after the ventricular complexes. These possibly represented sinus impulses elicited mechanically by the ventricular contractions. The ventricular complexes showed an incomplete right bundle branch block with right axis deviation, and clockwise rotation of the frontal vector with displacement of the transitional zone to the left (V5–V6). The S-T segments and T waves were normal. There were no signs of ventricular hypertrophy.

Roentgenologic examination showed considerable enlargement of the heart. Its volume was estimated to be 950 ml, i.e. 600 ml per m² body surface area. The enlargement involved the right ventricle and, to a lesser degree, the right atrium. The pulmonary artery and its central and peripheral branches were significantly dilated.

When admitted to the thoracic clinic in October 1961 the patient had moderate ankle edema. Otherwise the clinical examination merely confirmed previous findings. The heart rhythm at rest however was regular sinus bradycardia with a frequency of about 50 beats per minute (Fig 2, 1961). Under orthostatic conditions the arrhythmia appeared and then showed about the same variations as those previously noted. At an *exercise tolerance test* the ECG reaction was normal and the patient was able to work at an intensity of 600 kpm/min with a heart rate of 1?0 beats/min in steady state. Having performed the prescribed 6 minutes on this load and before continuing at a higher load, she interrupted the test because of tiredness in the legs. The sinus rhythm remained during and after the test and 10 minutes

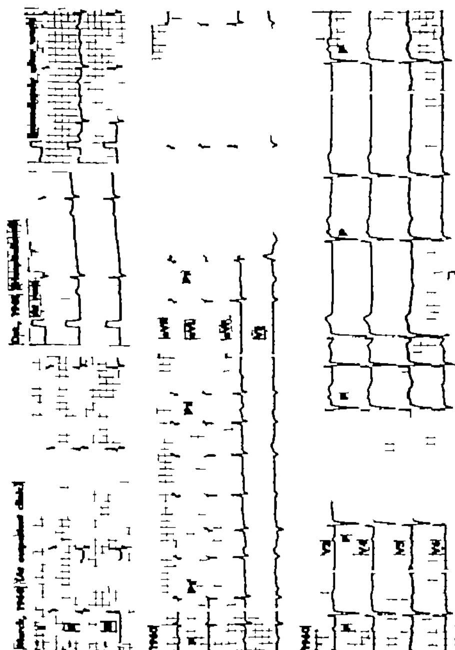


Fig. 2. ECG of the mother (Case 1). All 1960 recordings were obtained at single visit to the outpatient clinic. For further comment see text.

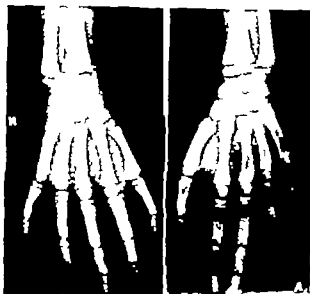


Fig 3 The hand of the son (Case). I both hands, the trapezium (os multangulum majus) is displaced distall The resultant distal displacement of the first metacarpophalangeal joints is accentuated on the right hand by the increased length of the 1st metacarpal. This metacarpophalangeal joint is in line with those of the other fingers. On external examination the apex of the first interdigital left is seen t be equidistal with the others. Compared t those on the left side, all primary bone centers on the radial aspect of the right forearm, wrist and hand re obviously hypoplastic.

later the pulse rate was well restit ted to 60 beat per minute The test indicated a normal physical working capacity from both circulatory and respiratory points of view

Heart catheterization wa performed following percutaneous introduction of the catheter into the right femoral ein as the patient seemed to have no arm eins suitable fo catheterization. Oxygen saturation conditions indicated a large left-to-right shunt t the atrial level. The min t volume in the systemic circuit wa calculated to be 4.. liters and that in the pulmonary circuit 1 .8 liters. The heart frequency was constant at 52 beats per minut and arterial oxygen saturation was 97% *Angio-cardiography* was not performed.

In November 1961 *surgical closure of an ASD* (secundum type) was made by open heart surgery under moderate hypothermia. The immediat post operative course wa uneventful apart from an increased tendency to intermittent arrhythmia showing further variations. Two months after operation, the patient general condition wa good, and roentgenologic examination showed significant decrease in heart volume

Case 2

G L., a boy born in 1951 son of M H., was healthy and developed normally as baby At the age f 4 years he had scarlet fever and was then found t have heart murmur During the following years, it was noted that he tended to avoid strenuous play with other children. He complained of dyspnoea nd headache on exertion but had no other definit ymptoms of heart disease In September 1958 he was admitted to the pediatric clinic for investigation

Physical examination showed the boy to be f normal height but somewhat slender build. (Age 7½ years, height 119 cm weight 19.3 kg) The palat was high and arched, and the shoulders were displaced forward. Roentgenographic examination, however failed to reveal any qualitative anomaly of

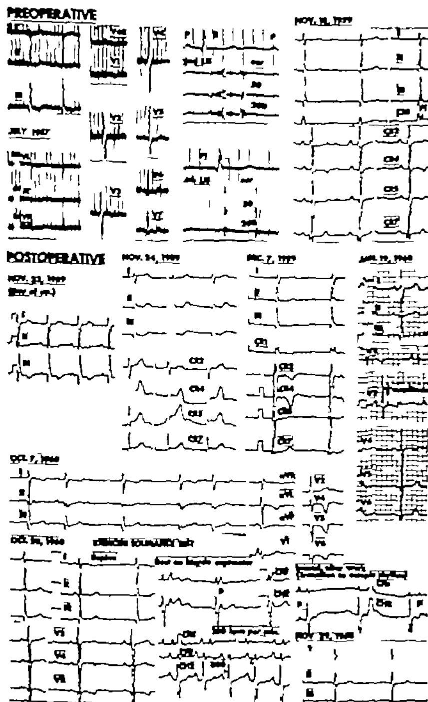


Fig. 4 ECG of the son (Case 2). See text for comments.

the shoulder girdle. On both hands the thenar eminences were hypoplastic and abnormalities of both thumbs were noted. The right thumb had two phalanges but was otherwise similar in shape and position to the abnormal digit seen on the mother's left hand. The left thumb was similar in most respects but was appreciably thicker than normal. Radiological examination showed in addition bilateral irregularities of the carpal and 1st metacarpal bones (Fig. 3).

Heart. The left hemithorax was somewhat more prominent than the right. Increased pulsations were seen and palpated along the left sternal border. A harsh grade 4 systolic ejection murmur was heard over the pulmonary region, and the second sound in this area was split (0.04 sec) with both components accentuated. At the lower left sternal border a weak mid-diastolic murmur was heard.

ECG showed the same type of ventricular complex as that observed in the mother. *The P waves over the right precordium and* in lead II were high and peaked as in enlargement of the right atrium. As a rule there was no evidence of arrhythmia. However, at an examination in 195[illegible] the ECG lead II recorded *simultaneously with the phonocardiogram* occasionally showed a flattening of the P wave (Fig. 4). Furthermore, at preoperative examination in November 1959 rhythm disturbances were recorded at the *beginning of a routine ECG*. *During one* period, variations of the P waves occurred so that it was sometimes impossible to identify them, whereas sometimes an ordinary P wave occurred in the S–T interval (Fig. 4 lead I, III and CR1). During another period a regular rhythm, elicited by an ectopic auricular pacemaker was predominant (P axis of the P wave −60°, AV conduction time 0.14 sec; not shown in figure). Finally after a few minutes of recording a regular sinus rhythm was established and persisted for the remainder of the examination (P axis of the P wave +60°, AV conduction time 0.19 sec; shown in leads CR–CR Fig. 4).

Roentgenologic examination of the heart revealed the same picture as in the mother. The heart volume was 500 ml, corresponding to 610 ml per m² body surface area. At *heart catheterization* the arterial oxygen saturation was found to be 99%, whereas in the pulmonary artery it was 8[illegible]% and in the superior vena cava 70%. These findings indicated that the flow in the pulmonary circuit was slightly more than twice that in the systemic circuit. The systolic pressure in the right ventricle was 31 mm Hg and in the pulmonary artery 27 mm Hg. By *angiocardiography* from the left atrium an ASD of the secundum type was demonstrated.

In November 1959 surgical closure of the ASD was performed under hypothermia. The immediate postoperative course was clinically uneventful, but a series of ECG recordings obtained between 1 and 14 days after operation (Fig. 4, Nov. 4 and Dec. 7) showed a consistent arrhythmia. The P waves occurred at varying intervals after the QRS complex and were sometimes of ordinary shape. The ventricular rhythm was regular and the rate was apparently not materially influenced by the ectopic impulse formation. During these two weeks, ventricular repolarization disturbances were seen *in left precordial leads*. These consisted of initial S–T elevation with subsequent flattening of the T waves progressing to deep negativity.

Following the boy's discharge from the hospital, the parents were impressed by his increased well-being and physical activity. At a progress check in January 1960 [illegible] months after operation, the physical signs of the ASD had disappeared, the S–T and T changes *had been normalized* and the rhythm was normal. The P waves over the right precordium, however, were very *high* and peaked, and the heart volume had not significantly diminished since operation. In February, *July and September* of the same year the patient had episodes of fever lasting for some days. On each occasion these were initially associated with pain in the precordium and one or both shoulders. In connection with the *last of these febrile attacks* he was admitted to the Pediatric Clinic, the

..ythmia had reappeared and ECG showed ..iphasic T waves over the left precordium. ..ring the subsequent few days progression f the T wave changes was noted, until they ..ecame deeply negative as they had been in ..he immediate postoperative period (Fig 4, ..let. 7). Later the S–T and T changes were ..nce more normalized. The heart rhythm ..t rest also reverted t normal but when .. was not complete and under orthostatic ..onditions, the arrhythmia reappeared. An ..xercise tolerance test was performed on ..let. 20 (Fig. 4) On moderate physical work ..he rhythm was normalized and remained so ..uring submaximal work. When work was ..topped, transition to ectopic rhythm oc ..urred.

During the following 1½ years the boy was .. of symptoms. A control examination ..s made at the Outpatient Clinic in April 1962. The physical findings were normal ..part from moderate parasternal pulsations ..nd split second sound. The pulmonary ..ystolic jection murmur was hardly audible ..he relative heart volume was estimated to ..0 ml per m body surface area. As the .. frequency at rest and during stan ..dized work was relatively low the in ..reased heart volume seemed to be related .. correspondingly greater ffective stroke ..lume as is found in cases of bradycardia ..e to complet AV block. At rest the heart ..uency was around 50 and at loads f 50 300 and 450 kpm/min it was 76 108 ..d 142, respectively A at previous exami- ..ons, sinu rhythm was present at rest ..d during work, but arrhythmia occurred .. orthostatic conditions before and ..fter work. Before work, the position f the ..y P waves shifted repeatedly in ..y suggestive f normal sinus rhythm lter ..ating with mechanical activation f the ..nus node by ventricular contraction. Other ..ariations such as deformed P waves and P ..waves occurring simultaneously with the ..RS complex were also seen. After work, the ..CG pattern was suggestive f sinus arrest .. alternatively sino-auricular block with ..onal doubling f the P–P interval and ..ormal AV conduction.

Comment

The pathological features of these two cases strikingly resemble those described in previous reports [4 5]. In both cases the atrial septal defect was of the secundum type The occurrence of the condition in a further parent–child constellation agrees with the theory of a dominant mode of inheritance This type of inheritance is also thought to be operative in some families showing multiple occurrence of isolated atrial septal defect [2 3 8 9 10] The thumb deformity described as characteristic of this syndrome was found on the mother s left hand and was almost reproduced on the hands of her son. Total absence of a thumb as noted on the mother s right hand was also observed in one member of each family previously described. The tendency to skeletal irregularity thus showed a predilection for a particular portion of the hand and at the same time a wide variation in manifestation from case to case. Such a variability is comparatively often seen in dominant gene effects As has been previously reported [1] the karyotype of the boy showed no abnormality The bizarre type of arrhythmia found in both cases i similar to that which has been previously reported [4] The common denominator seems to be a sinus bradycardia with prolonged AV conduction time and a tendency to inhibition of normal atrial activation because of sinus arrest or sino-auricular block. An ectopic focus may be activated in the auricular wall or more commonly in the AV conductive system without retrograde activation of the auricles. In such instances, mechanical activation of the sinus node by the ventricular contra tion seems often to take place.

The variations of this arrhythmia under different conditions are somewhat similar to those observed in chronic supraventricular tachycardia of the repetitive type [6 7]. Thus arrhythmia may or may not be present at complete physical rest and, if not it may be provoked by orthostatic conditions During physical work the rhythm is likely to return to normal, which might perhaps be taken as an indication of its benign nature Its occurrence even during prolonged and complete physical rest is probably dependent to a certain degree on psychological factors but may also be related to somatic disease In the boy reported here the tendency to ectopic rhythm was highly exaggerated in connection with repeated episodes of the so-called postpericardiotomy syndrome This syndrome which includes all the clinical, roentgenologic and electrocardiographic manifestations of a benign aseptic pericarditis, is also known to be often associated with arrhythmias of different kinds. It seems possible that it influences the nervous regulation of heart rhythm.

The syndrome of atrial septal defect and hand abnormalities described here must, obviously be considered to result from a disturbance of cardiac and skeletal formation From circumstantial evidence it would even seem reasonable to postulate a microscopic malformation as the underlying cause of the arrhythmia It would then be possible to consider that all the clinical features of the cases presented here constitute a pure malformation syndrome

Summary

The so-called atrio-digital dysplasia or Holt–Oram syndrome consists of atrial septal defect a tendency to cardiac arrhythmia and characteristic skeletal malformations involving particularly the thumbs It has previously been described in two families and seems to be transmitted as a dominant trait The present report describes its occurrence in a mother and son both of whom have been successfully operated upon for the atrial septal defect. The nature of the cardiac arrhythmia and its dependence upon different circumstances are discussed.

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The Pediatric Society of Southern Sweden

Meeting May 6 1962

Astrup: Micrognathia and its treatment

Six cases of micrognathia have been d at the Clinic, one f these with ontinuous aeration by t be in the nasoph-nx. The effect f this treatment was atisfactory (Will be published in detail another journal.)

Silver: Three uncommon cases of he- diseases

(1) *A case of Evans syndrome.* A 5-year-old rl was hospitalized after having exhibited disposition to bruising for a couple of nths. She had moderately lowered values hemoglobin and red blood cells, slight terus and a low value of haptoglobin in serum. There was pronounced thrombo-ytopenia but no splenomegaly. Cortisone erapy for 3 months did not produce any orthy effect on the blood values, and fore splenectomy was performed. There-ter the red blood cells and thrombocytes ng the course of a few months rose t ly normal values and the disposition to ising receded. Evans has discussed in 44 and 1933 autoimmunization the ne of hemolytic anemia and thrombocy in cases where both symptoms occur the same time, but also in thrombocyto- alone .g., idiopathic thrombocyto- purpura.

(2) A case f von *Willebrand' disease.* A -year-old boy with hemorrhagic symptoms bundantly occurring in the family. Further amilial investigation is in progress. (Will be ublished in detail in another journal.)

(3) A 9-year-old boy with prolonged bleeding time as a consequence f *reduced thrombocytic adhesion.*

B. Carell: Conn s syndrome

A 3-year-old girl was found t ha e an aldosterone producing adrenocortical ade noma. She was operated, after which she recovered completely. (Will be published in detail in another journal.)

S. Aronsson: A case of transplacental tumor metastasis

A 27 year-old woman was delivered with out complications one month before full term. The child, a girl, weighed 2 1 kg. After parturition the mother became higly febrile and died 4 days later. The autopsy revealed extensive metastases of malignant me-lanoma. N primary tumor was discovered. The child was in good health until 9 weeks f age when a growth was detected in the musculature of the right thigh. She was therefore admitted to Kristianstad Hospital. On examination two firm well-delimited masses, one the size f plum and the other the ze of walnut were palpated in the musculature of the right thigh and leg. In both temporal regions the patient had a pea-sized, firm, bluish-red infiltration. In the left gluteal region a walnut-sized mass was palpated. Examination f the eyes yielded normal findings. Roentgenography f the lungs revealed a couple f rounded paren-chymal lesions, a little more than the size f a thimble. All the laboratory values were normal with the exception of the sedimenta

tion rate of up to 45 mm. No melanuria could be demonstrated. Biopsy of the tumor in the right thigh musculature showed necrotic tissue containing melanin positive pigment. There was no vital tumor tissue. During a month's sojourn at the hospital the girl recovered without therapy. The skin and muscle tumors as well as the changes in the lungs disappeared. In a follow-up examination, at 18 months of age the girl was found to be in good health without any symptoms of tumor recidivation. The sedimentation rate was 7 mm.

Per Selander, Malmö

NEW BOOKS RECEIVED

Books received by the Acta Paediatrica are acknowledged under this heading. Selected books will be reviewed in subsequent issues as space permits.

Hypertrofisk Pylorusstenose. Olaf Steinicke: Universitetsforlaget, Aarhus, 1962.

Basic Facts of Allergy. R. Voorhorst. H. E. Stenfert Kroese N.V., Leiden, 196–. Price Fl. 34.

Pediatrics. E. Holt. R. McIntosh and H. Barnett. 13th Ed. Appleton-Century Crofts, New York, 1962.

Advances in Pediatrics. Vol. XII. S. Z. Levine: Year Book Medical Publishers, Chicago 1962. Price $10.

The Foundation on The Exocrine Pancreas. A.V.S. de Reuck and Margaret P. Cameron (Ed.). J. & A. Churchill Ltd., London, 1962. Price 55s net.

Growth and Development in Children. E. H. Watson and G. H. Lowrey: 4th Ed. Year Book Medical Publishers, Inc., Chicago, 1962. Price $7.75.

The Adrenal Cortex. F. T. G. Prunty (Ed.): British Medical Bulletin 18. No. 2. May 1962.

Hospitals and Children. A Parent's Eye View. James Robertson (Ed.). Victor Gollancz Ltd., London, 1962. Price 18s net.

Rutgendiagnostik der Säuglingspneumonien. K. Gefferth. Akadémiai Kiado Verlag der Ungarischen Akademie der Wissenschaften, Budapest 1962. Price $12.

Die Tuberkulose der endothorakalen Lymphknoten im Kindesalter. O. Görgényi-Göttche: Publishing House of the Hungarian Academy of Sciences, Budapest 1962. Price $1.50.

On the Ontogenesis of the Human Gastric Epithelial Cells. P. Salenius. Acta Anatom. Suppl. 46. 1962. S. Karger. Basel, 196–. Price sF 14.—

Kongenitale Störungen des Wasser- und Elektrolythaushaltes. H. Hungerland and J. Brodel (Ed.): Springer Verlag. Berlin, 1962. Price DM 39.60.

Chromosomes in Medicine. John L. Hamerton. The National Spastic Society London. William Heinemann Medical Books Ltd., London, 196–. Price $6.

Praktikum der Schutzimpfungen. Kurt Hartung (Ed.): H. Hoffmann Verlag. Berlin, 1962. Price DM 18.30.

Transfusions Foeto-Maternelles. Colett Devin. Thèse. Lille 196–.

Reading Disability. Progress and Research Needs in Dyslexia. John Money (Ed.): The Johns Hopkins Press, Baltimore 196–. Price $5.

Pediatric Surgery. C. D. Benson. W. T. Mustard, M. M. Ravitch. J. and K. J. Welch. Two volumes. Year Book Medical Publishers, Inc. Chicago, 1962. Price $42.

Lessons from Animal Behaviour for the Clinician. Barnett, S. A. (Ed.): Little Club Clinics in Developmental Medicine. No. 7. William Heinemann Ltd, London, 1962. Price 12s 6d.

Acute Hemiplegia in Childhood. Bax, Martin and Ross, Mitchell (Ed.). Little Club Clinics in Developmental Medicine. No. 6. William Heinemann Ltd, London, 1962. Price 17/6.

BOOK REVIEW

Lewis & Barness Manual of Pediatric Physical Diagnosis

Year Book Medical Publishers Inc., Chicago, 1961 Second edition. Price $4.00

"Since steroids and antibiotics have not yet replaced the necessity of physical examination the purpose of this volume remains—to indicate the differences in physical diagnosis between children and adults," the author states in the preface to the second edition. This little book is arranged in a simple and untheoretical way. First short *chapters on Approach to the Patient*, Measurements, General Appearance, Skin, Lymph Nodes; thereafter the signs and symptoms are described in a topographical arrangement: Head and Neck, The Chest, The Abdomen, Extremities, Spine, Joints and Muscles, Neurological Examination. A special chapter is then dedicated to the Examination of the Newborn where the same topographical arrangement is again used. Finally three appendices are included: A Record of Physical Examination useful for a Scandinavian having to give a case report in English; a list of Some Rare Syndromes with Characteristic Appearances; and Growth Charts. The practical advice is good and the evaluation of the findings is skilful and restrained. "Craniotabes is found in premature infants, in some normal children under six months of age, in babies who lie constantly on one side of the head, and in children *with rickets, syphilis, hypervitaminosis* A and hydrocephalus."

This little book must be very helpful for the freshman, but also, as revision, for trained pediatrician.

Gert Sylow Sandwall

The Adrenal Cortex. scientific ed. F. T. G. Prunty

British Medical Bulletin *18* No. 2 May 1962

The British Medical Bulletin appears each year with three numbers dealing with different topics of medicine and related fields. The publication contains excellent reviews *with contributions of leading British authors*. The May number of the Bulletin is no exception to this rule. The volume is devoted to the adrenal cortex with the first chapters dealing with the biogenesis and synthesis of adrenocortical steroids and the interesting problems of adrenal steroid production by the placenta, foetus and newborn. The next part contains chapters covering the morphology of the adrenal cortex in vertebrates including man. The physiology is treated in a section with chapters on, for example, mechanism of adrenocortical control, metabolism of steroids and their action at the cellular level. In the last mentioned chapter Bush concludes that in spite of intensive work on the problem it remains one of the major challenges of physiology and biochemistry. Disorders of biosynthesis in man and recent methods for the investigation of disorders of the adrenal cortex are two chapters of special clinical interest. The critical evaluation of present methods and their application to different diseases related to the adrenal cortex is of great value for all, including paediatricians, who have to diagnose and treat endocrine disorders. The last three chapters are devoted to problems concerning aldosterone. For those who are not familiar with the steroid nomenclature a glossary of terms used in the volume is of great help, and each chapter is followed by adequate references.

In his introduction Professor Prunty expresses "the earnest hope of the planning committee that the volume will be rewarding to its readers, that to some it will simplify and to others act as a fulcrum about which further research will develop." There seems to be little doubt that these tasks are accomplished in an excellent way by the experts who have contributed.

Carl Gustaf Bergstrand Stockholm

Hettinger (Ed.) Beiträge zur Klinik ? Pathogenese der Coeliakie
Karger Basel. 196.. Price SFr 15.—

r is a compilation of papers read and ssed at symposium on coeliac disease ld in Switzerland in May 1961 with icipants from Belgium, England, Ger y Holland and Switzerland. The sym ium was sponsored by Galactina and maiz AG t commemorat its 60th ersary In a historical review Fanconi mpares the old concept f "Verdauungs ffinenz with the stem f a tree with eloping branches, the youngest f which gliadin hypersensitivity saccharase and tase deficiency and steatorrhoea combined h lack of β-lipoproteins. The chapters aling with diagnosis and differential gnoses give good summary f the char eristics of the disease One diagnosis en special attention is Lamblia infesta n. As regards the laboratory tests Käser rns against placing too much confidence the vitamin A and xylose tolerance tests d stresses the value f following the fecal A comparatively new test described Gruttner is the paper chromatographic centration of a characteristic peptide in patient's plasma after a test dose of adin. This method should be of value pecially together with mucosal biopsy dings in abortive forms f the disease cosa biopsies are not discussed in any all but the typical findings are mentioned. month is the usual period necessary for of real improvement t appear on en free vitamin enriched diet which uld be continued for two years. If a apse occurs when gluten is then tried— ich is expected to happen in half f the the patient should start another years period on gluten free diet The ue of supplementing the gluten free diet ly ith fat containing unsaturated fatty ds is evident from the chapter by Fer es, van de Kamer and Weijers on selec reesorption of fatty acids. The prognosis low good quoad vitam. Some patients will nue t have symptoms as adults if not on gluten free diet—43% f adults with sprue are found t have had symptoms in childhood. There seems t be little doubt that early adequat treatment enables the patient to grow at normal rat In a hapter dealing with causal and conse quential factors in coeliac disease Frazer gives a clear picture of what is known today about the active factor in gliadin. It is thermost ble capable f initiating stea torrhoea in patients with coeliac disease in remission on adequat diet it is inactivated by incubation with normal intestinal mucosa but not with mucosa from patient with gluten intolerance and seems to interfere with the release f acetyl choline H con siders gliadin intolerance to be the major causal factor in coeliac disease but hol ls t to be likely that other factors exist which may precipitat the disease by damaging the intestinal mucosa. The role f heredity is well known allergic factors are still difficult to evaluate. Apart from the field of mucosal biopsies this symposium gives a good review of the main aspects f coeliac disease

B Werner Stockholm

S Z. Levine (Ed.) Advances in Pediatrics, V L XII
Yearbook Medical Publications Inc Chicago, 1962

This volume follows the same lines as the previous ones. It is a collection of short monographs of current pediatric problems, written by experts in the respective fields. The standard of the articles is f the same level as one is accustomed t find in this series, and the editor and the publishers must be congratulated on the result The titles of the articles are: Viral Encephalitis, Bilirubin Metabolism with Special Reference t Neonat l Jaundice Chemotherapy f Neoplastic Diseases in Children, the Teaching of Pediatrics and the Role of the Pedia trician in Developing Countries, Viral In fections of the Fetus and the Premature and Newborn Infant and Physiology and Pathology f Calcium and Phosphat Metabolism.

G. Maggi: L'Aminoaciduria Normale e Patologica del Bambino. (Normal and Pathological Amino-aciduria in Children.)

The author gives a brief but somewhat incomplete summary of our present knowledge of normal and pathological urinary excretion *of free amino acid* with particular reference to children. With the ion exchange chromatographic technique according to Stein and Moore the author has studied the amino acid excretion in six normal children, in three prematurely born infants and in nine children *suffering from* various diseases including protein malnutrition (four cases) and cystin storage disease (two cases). No entirely new contributions are given. The results, as well as the summary, are given in Italian, which renders the reading difficult.

R. Jagenburg, Göteborg

A. Fioretti: Die Gaumenmandel. Georg Thieme, Stuttgart 1961

This is a German translation of an Italian monograph from the University of Padua from 1957. The greater part of it consists of a very thorough survey of comparative anatomy of the tonsils—their histology, embryogenesis and pathophysiology. This part does not seem to be of any great interest to the clinician. The author points out that tonsils in early childhood are producers of antibodies, but that this function very soon diminishes, and they then become the site of focal infections or producers of auto-antibodies. The last chapter of the book, "The focal infections of the tonsils" by M. Arslan, is of somewhat greater clinical interest, at least for the ear, nose and throat specialist, and deals, *inter alia*, with the indications for tonsillectomy, which seem to be about the same as those in this country.

G. Hedvall, Sundsvall

ANNOUNCEMENTS

A Request

Professor Hans Selye, Director of the Institut of Experimental Medicine and Surgery, University of Montreal, has requested the readers of *Acta Paediatrica* to send all available reprints of their work, especially those dealing with Endocrinology and Stress, to: P.O. Box 6128, Montreal 26, Canada. *In this way he hopes to rebuild the* Institut library which suffered extensive losses through fire.

Congresses

The *Second European Congress of Child Psychiatry* will be held in Rome May 21st to June 4th, 1963, with Professor Giovanni Bollea as President. The main topics are: Character disorders in childhood and adolescence, Follow up of child psychosis, Language troubles and development of intellectual and extralinguistic functions, and Family mental deficiency. Further information is given by the General Secretary, Professor Arnoldo Novelletto, C.P. 7130, Roma Nomentano, Rome, Italy.

The *Second International Congress of Nephrology* will be held in Prague August 25th to 29th, 1963, with Professor J. Brod as President. There will be a number of symposia concerning important recent problems of renal physiology and round-table discussions on *Transport Phenomena*, The Kidney in Pregnancy, Chronic Pyelonephritis, Renal Hypertension and Dialysis Treatment of Chronic Renal Failure. For further information write to the General Secretary, Dr. J. Jirka, Institut for Cardiovascular Research, *Prague 4-Krc, Czechoslovakia.*

Acta Pædiatrica 52: 129—132, March 1963

From the University of Bergen, School of Medicine Department of Pediatrics (Head Professor Alfred Sundal)

Congenital Afibrinogenemia

by SVEIN OSEID and HARALD MORTEN SVENDSEN

A congenital lack of fibrinogen is a very rare cause of abnormal bleeding tendency in childhood, and since the first description by Rabe & Salomon in 1920 [10], about 40 reports of this disorder have appeared in medical literature. The disease has been classified as an inborn error of metabolism [11] transmitted by means of an autosomal recessive gene [2, 4, L.], which causes a disturbance of fibrinogen synthesis in the liver [1].

Two cases from Norway, a brother and a sister, are described, as this condition has never been reported previously from Scandinavia, and because it has been possible to study the family in some detail.

Case Reports

1. B.L., boy, was born on April 4, 1949. When he was 3 days old a severe umbilical hemorrhage occurred which continued for a further 7 days. At the age of 3 years it was noted that the boy bled easily from minor wounds and skin lesions and, following a moderate injury with prolonged bleeding, he was admitted for the first time to the Children Department, University Hospital, Bergen, in March 1953. Hemorrhage of varying severity, sometimes requiring blood transfusions, has necessitated his admission to hospitals on several subsequent occasions, but spontaneous hemarthrosis, epistaxis, hematuria, or gastrointestinal hemorrhage has never been observed. The true nature of his condition was first recognized in 1957. Apart from his bleeding disorder he has been healthy and has shown a normal mental and motor development.

The patient was readmitted on August 24, 1961, aged 11½ years for dental extraction of a carious tooth. Physical examination revealed a well-developed, healthy looking boy, but with ecchymotic areas on both upper and lower limbs. On his lower lip he had a small ulcer which bled easily. Except for a carious premolar tooth, no other abnormalities could be found.

On examination of the blood the most striking feature was its complete incoagulability. Whole blood was drawn into a sterile test tube and incubated at 37°C. The sample was inspected after two, four, eight, twelve and twenty four hours. No clot formation could be observed. Neither heating the plasma to 60°C nor the addition of thrombin (100 NIH units per ml) produced coagulation, and immunoelectrophoretic estimations failed to reveal fibrinogen in the plasma. There was no increase of plasma fibrinolytic activity. Additional blood tests are shown in Table 1.

Following these investigations the carious tooth was extracted under local anesthesia and the empty socket was filled with spongostan and sutured. Moderate bleeding from the wound continued for ten days.

2. L.L., sister of B.L., was born on June 30, 1957. She also suffered from a severe umbilical hemorrhage a few days after birth, and later developed large ecchymotic lesions. She has a tendency to prolonged bleeding

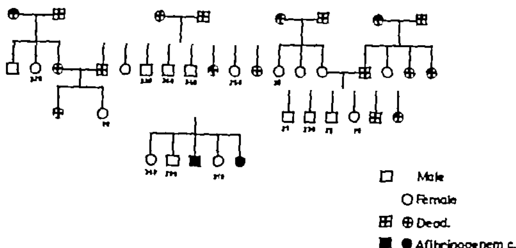


Fig. 1. Genealogy of cases reported. Number indicat fibrinogen level (mg %).

from minor wound although she has never required blood transfusions. She has been healthy with normal mental and physical development; hemarthrosis, epistaxis, urinary or gastrointestinal hemorrhage has never occurred.

She was admitted for the first time together with her brother on August 4 1961. Physical examination revealed a 4-year-old well developed and healthy looking girl with several small subcutaneous hemorrhages on her legs. No further abnormalities were detected on full clinical examination. The results of the coagulation test and immunoelectrophoretic fibrinogen determination were identical with those of her brother. Other important laboratory data are shown in Table 1.

TABLE 1

	B. L.	L. L.
Hemoglobin	86	74
RBC/mm³	4,070,000	2,820,000
WBC/mm	9 000	8,400
Platelets/mm	*72,000	*63,000
Sedimentation rat	1 mm/h	3 mm/h
Tourniquet test	Normal	Normal
Bleeding time:		
Duke method	> 10 min	> 10 min
Mod. Ivy method	> 20 min	> *7 min
Proaccelerin	150	110
Proconvertin	88	90
Prothrombin %	68	83
AHG %	62	—

Comment

Although congenital afibrinogenemia has been extensively studied there still remain certain unsettled problems to which attention should be drawn.

Frick & McQuarrie (4) in their excellent review of this disease state that hemarthrosis, the typical manifestation of hemophilia does not occur in congenital afibrinogenemia. However repeated spontaneous hemarthrosis has been described in at least two patients (5, 12) though not in the children reported here. Hemarthrosis does not therefore exclude the diagnosis of congenital afibrinogenemia.

Most authors report a normal bleeding time in congenital afibrinogenemia, whereas in each of our patients two estimates of the bleeding time using Duke's and a modified method of Ivy as described by Borchgrevink & Waaler (3), were definitely prolonged. Frick & McQuarrie suggest that a prolonged bleeding time is due

to faulty technique. Their view is in accordance with an interesting observation by the children s mother She told us that the bleeding from very small and superficial skin lesions stopped after a few minutes. If these lesions were left alone under a soft cover they would heal and would not cause more trouble. But if the lesions were disturbed more or less briskly a secondary bleeding would ensue A similar observation is reported by Morita & Kagami [8]. These observations indicate a normal primary and a prolonged secondary bleeding time as seen in other coagulation disorders, such as in hemophilia and proaccelerin deficiency It is essential in the modified bleeding time test of Ivy to produce very superficial cuts, approximately one mm deep Although great care was taken, it might be that the cuts were made too deep in the present cases. Thus, the prolonged bleeding time can possibly be ascribed to the faulty technique of an inexperienced examiner

The hereditary nature of congenital afibrinogenemia seems to be established. The mode of inheritance however is still a matter for discussion, although a rare recessive utosomal trait seems to be responsible The following facts support this therory

1 Consanguinity is found in bout 50 % of the reported cases with cousin marriages occurring in parents and grandparents [12]

2 Several siblings of patients with congenital afibrinogenemia have died in the newborn period from severe umbilical hemorrhage These siblings were probably suffering from the same disease but on only two occasions has this been proved [3 5].

3 Some authors have found hypofibrinogenemia in one or more relatives of patients with congenital afibrinogenemia [3 4 7] and it is suggested that the heterozygous carrier state discloses itself in this way This feature is well known from other diseases with a recessive trait as for instance galactosemia.

In the cases presented, consanguinity of parents or grandparents could not be found and the family history did not reveal any other affected individuals (Fig 1) The plasma fibrinogen levels in relatives of the patients were determined by the photometric method described by von Porat [9] and modified by Goe [6] (normal range of variation is 200–400 mg/100 ml) Plasma from the parents, three siblings and eleven other relatives who could be traced, has been examined in each case the plasma fibrinogen level was within normal limits (Fig 1) The only circumstance in the present cases which betrays the hereditary nature of the disease is its occurrence in a brother and a sister This seems very unlikely to be a chance finding

Summary

Two patients, brother and sister suffering from congenital afibrinogenemia are reported. This condition has previously not been described from Scandinavia. Both suffered from severe umbilical hemorrhage soon after birth and a continuing bleeding tendency The diagnosis has been proved by coagulation tests and immunoelectrophoretic fibrinogen determinations. The hereditary nature of the disease is briefly discussed. Plasma fibrinogen estimations were made on 17 relatives but this failed t demonstrate any heterozygous carriers within the group

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Sexual Maturation of Israeli Boys of European and Middle Eastern Origin Preliminary Study

by ZVI LARON

Whether climate and race affect the time of adolescence is a matter of dispute [5]. Economical and social status, as well as nutritional factors, are difficult to disentangle from other geographic conditions. The still primitive conditions prevailing in many populations living in warm countries, including the lack of registration of the birth date, are hindrances in performing studies relating development to chronologic age.

The widespread belief quoted in text books [4] that children mature earlier in the tropics than in temperate climates, has been challenged [1 2]. Mills [3] even concluded that sexual maturity in tropical countries comes later than in temperate regions.

As boys lack a well defined period corresponding to the menarche in girls, studies of the age of sexual maturation in boys are very scant. Ellis [1], studying small groups of Nigerian school boys from a high socio-economic class, found that their degree of sexual maturation compared agewise with that of school boys from England.

The mass immigration into Israel during the last 14 years, comprising Jews from European as well as African and Asian countries, presents a unique opportunity to study the sexual maturation in different communities. We shall report the results of a pilot study comparing the degree of sexual maturation in Jewish boys of European and Middle Eastern origin.

Material and Methods

Two hundred and forty two healthy boys were examined in schools and the following details were registered: (1) lack of any secondary sexual signs; ( ) presence f pubic hair (3) presence of axillary hair; and (4) presence f facial hair (moustache)

The age of the children ranged between 9 and 16 years. Only hildren whose dat f birth was known are included in this study Their distribution according to age and their classification is shown in the table. Under European are classified children born to parents who emigrated t Israel from Europe during the last 20 years. Under Mid Eastern are classified children who themselves or whose parents emigrated t Israel from Yemen, North Africa, Iraq, Kurdistan, Syria and children whose parent were born in Israel. Children of mixed marriages are not included.

Results and Comments

The results of the survey are graphically illustrated in Figs. 1 to 4 It is evident that

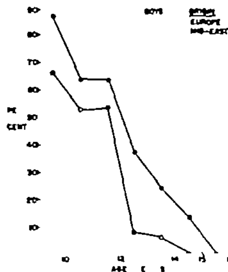


Fig 1

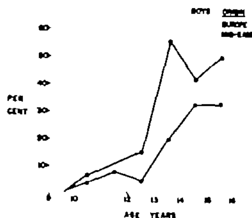


Fig 3.

boys of Mid Eastern origin are sexually mature earlier than boys of European origin This is seen from the smaller percentage of boys with no sexual maturation among Mid Eastern boys at a given age and the presence of secondary sexual signs in a greater percentage of these children at a given age compared with their counterpart of European origin. We were also impressed by the fact that the Yemenite boys at the age of 16 showed almost complete sexual maturation, very rarely encountered among boys of European origin.

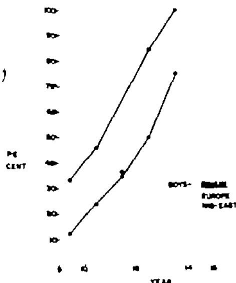


Fig. 2.

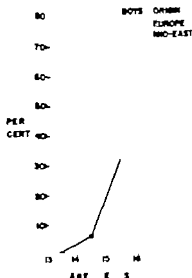


Fig 4

Table 1 *Age groups and number of boys studied*

Age group	European	Mid Eastern
9–10	33	12
10–12	51	26
12–14	49	29
14–16	18	20
Total	151	91

The results of this study showing that boys of Mid Eastern origin have a tendency to mature sexually earlier than boys of European origin, are in contradiction with the findings of Ellis in Nigerian boys [1], and with the prevailing opinion cited by Talbot *et al.* [4] that children in a warm climate mature earlier Our findings would rather favour a genetic cause for the difference in maturation in various communities.

Studies on a larger scale including laboratory studies of urinary gonadotrophins and sex hormone metabolites and related details on the socio-economic status, have been planned.

Summary

Two hundred and forty two Israeli boys aged from 9 to 16 years were examined for the presence of secondary sexual characters. It was found that boys born to parents originating from Israel or other Mid Eastern countries are sexually mature earlier than boys born to parents who *immigrated from Europe during the last 20 years.*

Acknowledgement

The author is indebted to Dr H. Heinrich, Dr B. E. Cohen and Dr H. Boichis for their permission to examine children in schools under their care.

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Bone Marrow Studies in Patients Suffering from Infections and Receiving Chloramphenicol

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Aplastic anemia has been reported in patients receiving chloramphenicol [.., 4 0 7 14] The *incidence of severe bone* marrow damage associated with chloram phenicol is not great Temporary ery throid hypoplasia [8 10 11 12] occasionally associated with thrombocytopenia [8] and leucopenia [10] due to chloram phenicol administration appears to be more frequent than the irreversible or slowly reversible bone marrow depression

Thus Rubin *et al* [12] using sensitive radio-iron techniques, found evidence for suppression of red blood cell production in 5 of 15 patients tested while Saidi and associates [13] reported morphologic changes in primitive red cells of the mar row in each of 10 patients who received 40–85 mg/kg of chloramphenicol per day for 4 to 27 days.

The purpose of this report is to present bone marrow studies in 45 patients suf fering from various infections and treated with chloramphenicol for a short period of time

Material and Methods

Forty five patient with various infec tious processes form the clinical material of this report Thirty were males and 15 females. Their age ranged from 2 months to 5 years (Table 1)

All patients except case 23 received 40 to 100 mg/kg per day of chloramphenicol (peroral administration chloramphenicol palmitate; intramuscular injection synthetic chloramphenicol; intravenous injection chloramphenicol glycinate) for a period of no less than ten and no more than twelve days.

The first bone marrow was obtained on admission, the second, on the last day of chloramphenicol administration, and the third ten days after treatment had been discontinued. Hemoglobin and reticulocyte count were taken every 4th day during the patient hospital stay Standard methods were used for blood and marrow studies and reticulocyt counts were made by the wet method

Results

The data on our patients are summarized in Table 1 Most patients had some degree of anemia on admission. This was of hypochromic type with a superimposed infection.

Examination of bone marrow prior to chloramphenicol administration showed depressed erythropoiesis in 6 patients (Cases 22, 23 26 29 31 and 33) from the infection alone No vacuolated bone marrow erythroblasts were seen.

Bone marrow counts on the last day of chloramphenicol administration showed that only two patients (Cases 19 and 23) had developed depression of erythro-

esis. Erythropoietic activity in Cases 26 29 31 and 33 returned to normal ɔ chloramphenicol administration, hile in Case 22 the depression of ery ropoiesis persisted. Vacuolization of urly erythroid elements was very un ommon. A significant decrease in reti ulocytes and hemoglobin was not ob- d during the course of chloram- col administration. Termination of e aplastic crises, was not followed by a gnificant increase in reticulocytes in 25 26, 29 31 and 33

Bone marrow counts obtained ten days chloramphenicol had been discon nued showed normal erythropoetic ac- ty except in Case 22. In this patient pression of erythropoiesis was still ent. In Case 41 depression of ery ropoiesis was now observed for the first . In both these cases the bone marrow d reversed to normal when the patients re examined in the out patient clinic one onth later

Discussion

Two types of hematological toxicity have n observed following the administra on of chloramphenicol, (I) severe fre- ently fatal, pancytopenia, and (II) mporary erythroid hypoplasia, associ- d with anemia and occasionally with rombocytopenia and leucopenia. Large ses of chloramphenicol (8–10 g daily) ere administered to patients with ad nced carcinoma by Krakoff *et al* [8]. the patients developed anemia with iculocytopenia nd a f w also had ucopenia and thrombocytopenia. How marrow examinations revealed nor cellularity with some minor abnorm ities in the myeloid elements With cessation of therapy peripheral blood changes returned to normal.

A comparable case to those reported by Krakoff *et al*., was published by Ozer *et al*. [10] In this case severe erythroid hypoplasia with maturation arrest, de crease in megakaryocytes and a bleeding tendency also occurred. Morphologic changes in the primitive red cells of the bone marrow were reported by Saidi *et al* [13] in ten patients who received 40–80 mg/kg of chloramphenicol per day for 4 to 27 days. No such changes were observed in 12 patients who received 11 to 45 mg/kg per day for 4 to 59 days. How ever Saidi *et al* did not obtain bone marrow aspirations prior to initiating treatment. Administration of chloram phenicol to normal individuals was not associated with morphologic changes in the primitive red cells of the marrow while all anemic subjects developed such changes, after being given chloramphen icol. Saidi *et al* concluded that the high incidence of hematologic abnormalities observed in anemic subjects in patients suffering from various infections, and receiving chloramphenicol, and the ab- sence of such changes in normal subject indicates the presence of host factors. The same workers as well as others [8 10], have pointed out that high doses of chloramphenicol are a factor in the produc tion of blood changes.

Morphologic abnormalities of the bone marrow similar to those described by Saidi and associates were reported by McCurdy [9]. Most of the patients he described were suffering from various infections. Ten of th fifteen patients had mild to severe pre-existing liver disease and one had hronic glomeru-

TABLE 1 *Clinical and laboratory features of 45 patients suffering from infections and receiving chloramphenicol*

Case no.	Age	Sex	Chloramphenicol mg per kg/day	Route of administration	% normoblasts in marrow P	% normoblasts in marrow E	% normoblasts in marrow A	Reticulocytes % P	Reticulocytes % E	Reticulocytes % A	Hemoglobin g % P	Hemoglobin g % E	Hemoglobin g % A	Diagnosis	Other drugs
1	3 yr	M	40	P.O	20	17	18	0.3	1.0	0.3	10.7	11.7	11.5	Pneumonia	
2	8 mo	M	40	P.O	14	17	1	0.6	1.0	2.0	10.9	10.4	10.7	Infection diarrhea	
3	10 mo.	F	60	P.O	1	1	20	0.8	1.0	1.2	11.6	11.3	11.3	Infection diarrhea	Neomycin-Mycostatin
4	5 mo.	M	50	P.O	18	19	20	0.2	0.2	0.4	8.9	8.7	8.8	Infection diarrhea	Neomycin
5	4 mo.	M	100	P.O	18	12	20	0.3	0.3	0.3	9.1	10.1	10.0	Infection diarrhea	Neomycin Penicillin
6	3 mo.	F	0	P.O	15	17	25	0.5	0.6	1.–	10.0	10.0	10.5	Infection diarrhea	Neomycin Mycostatin
7	5 mo.	M	60	P.O	26	23	20	0.3	0.2	0.9	11.2	10.7	11.0	Infection diarrhea	
8	9 mo.	F	60	P.O	18	1	4	0.3	0.4	0.6	9.4	8.9	8.9	Urinary tract infection	Streptomycin Penicillin
9	9 mo.	M	60	P.O	26	20	21	0.5	0.6	0.7	10.9	10.8	11.0	Infection diarrhea	Neomycin
10	5 mo.	M	100	I.M	8	23	22	0.2	1.0	0.5	8.9	8.3	8.2	Purulent meningitis	Penicillin-Sulfadiazine-Streptomycin
11	9 mo.	M	50	P.O.	3	27	4	0.7	0.5	0.5	8.9	9.4	9.6	Infection diarrhea	
1	4 mo.	M	100	I.M	18	1	26	0.–	0.1	0.5	11.8	10.7	10.7	Purulent meningitis	Penicillin-Sulfadiazine-Streptomycin
	10 mo.	F	60	P.O	23	22	4	0.3	0.5	0.4	11.4	11.3	11.3	Infection diarrhea	
14	4 mo.	M	70	P.O	15	14	16	0.–	0.1	0.1	11.6	11.4	10.9	Infection diarrhea	Neomycin
15	5 mo.	M	70	P.O.	20	16	17	0.1	0.2	0.3	9.1	9.7	9.7	Infection diarrhea	Neomycin Streptomycin
16	3 mo.	M	90	P.O.	17	18	18	0.3	0.4	0.4	12.0	11.4	11.–	Infection diarrhea	Neomycin-Penicillin
17	5 mo.	F	100	I.M.	15	20	23	0.5	1.0	0.8	6.0	7.8	7.8	Purulent meningitis	Penicillin-Streptomycin-Sulfadiazine
18	6 mo.	M	100	I.M.	14	20	20	0.–	0.–	1.0	8.6	8.0	8.6	Purulent meningitis	Penicillin-Sulfadiazine
19	2 yr	F	100	I.M.	15	2	20	0.1	0.01	0.3	6.0	6.0	5.6	Purulent meningitis	Penicillin-Sulfadiazine
20	5 mo.	M	100	I.M.	13	20	28	0.5	0.7	0.7	6.6	6.4	6.4	Purulent meningitis	Penicillin-Sulfadiazine
1	1 mo.	M	50	I.M.	23	16	18	0.5	0.4	0.4	11.3	10.5	10.9	Purulent meningitis	Penicillin-Sulfadiazine
22	14 mo.	F	60	P.O	4	2		0.4	0.1	0.3	12.0	10.55	9.7	Whooping cough	
23	3 mo	M	100	I.V P.O	19	6	15	0.5	0.2	0.8	9.17	8.7	11.5	Purulent meningitis	Penicillin-Streptomycin-Erythromycin

continued)

Sex	Chloramphenicol mg per kg/day	Route of administration	% normoblasts in marrow P	% normoblasts in marrow II	% normoblasts in marrow A	Reticulocytes % P	Reticulocytes % II	Reticulocytes % A	Hemoglobin g % P	Hemoglobin g % II	Hemoglobin g % A	Diagnosis	Other drugs
M	50	I.M.	15	20	24	0.5	0.64	0.6	12.7	13.3	13.0	Bacteriemia	Penicillin–Erythrocin
F	80	I.M.	5	18	20	0.3	1.0	1.0	6.4	8.0	8.5	Purulent meningitis	Streptomycin–Penicillin–Sulfadiazine
M	100	I.V P O	3	40	30	0.1	1.0	1.0	10 7	10.8	11.5	Sepsis	Penicillin–Erythrocin–Mycostatin
M	100	I.M. I.V	10	10	15	0.5	0.5	0.6	13.0	12.5	10.9	Sepsis	Penicillin–Erythrocin–
F	80	P O	17	13	14	0.8	0.6	0.6	7.5	7.8	7.9	Infection diarrhea	Neomycin
F	60	P O	5	15	16	0.5	1.0	0.9	11.6	11.0	11.0	Infection diarrhea	Neomycin
M	40	P O.	24	18	20	0.6	0.8	0.8	11.2	11.3	11.3	Infection diarrhea	
M	80	I.M. P O	5	28	30	0.3	0.5	1.0	10.4	11.–	12.–	Infection diarrhea	Neomycin
M	40	P.O.	16	13	16	0.4	0.5	0.5	9.0	9.5	8.8	Infection diarrhea	Neomycin
M	50	P O	5	10	12	0.3	0.2	0.4	9.0	9.2	10.5	Infection diarrhea	
F	80	P.O	16	35	30	0.2	1.3	1.3	8.0	8.9	10.0	Bronchopneumonia	Penicillin
M	50	P O	12	14	15	0.6	0.5	0.6	8.3	8.5	8.6	Bronchopneumonia	Penicillin
M	80	P O	17	34	37	1.0	1.5	1 7	11.6	10.3	8.8	Dehydration diarrhea	
M	60	P O	21	18	18	1.5	1.0	1.1	9.7	10.8	11.0	Infection diarrhea	
F	60	P O	16	22	20	0.4	0.8	0.8	11 6	10.5	10.5	Infection diarrhea	
M	60	P.O	16	15	18	1.0	1.0	1.0	8.7	8.2	7.8	Infection diarrhea	Streptomycin
M	70	P O	13	19	18	1.0	1.9	1.0	11.3	10.5	10.5	Infection diarrhea	Neomycin
F	70	I.M. P O.	18	28	0	1.3	1.3	0.2	12.2	12.3	11	Whooping-cough, Broncho-pneumonia	Penicillin Erythrocin
F	60	I.M.	17	20	20	0 4	0.5	0.9	7.8	9 5	8.9	Purulent meningitis	Penicillin Sulfadiazine
M	110	I.M.	19	20	+0	0.8	0 7	0 9	5.3	6.0	9.9	Purulent meningitis	Penicillin Sulfadiazine
M	100	I.M.	15	19	18	1 4	1.2	1 4	8.9	9.2	9 6	Purulent meningitis	Penicillin Sulfadiazine
F	60	P.O.	20	19	22	0.4	0.7	0.7	9 5	10 0	9.8	Infection diarrhea	Neomycin

or to chloramphenicol administration.
the end of chloramphenicol administration.
days after chloramphenicol had been discontinued.

lonephritis with uremia. Bone marrow aspirations were obtained in 5 patients prior to treatment

Our studies indicate that 40 to 100 mg/kg per day of chloramphenicol for about ten days is not associated with a high incidence of morphological abnormalities of the bone marrow nor is it associated with a significant decrease in hemoglobin level. Only two of our 45 patients developed erythroid hypoplasia and one of them received the drug for 20 days (Case 23)

In control studies performed by McCurdy it was found that morphological abnormalities of the bone marrow were not observed in two patients who did not develop anemia after three or more weeks of chloramphenicol. The low incidence of bone marrow changes in our patients may be related to the fact that none of our patients developed a significant decrease in hemoglobin level while receiving chloramphenicol. This may be due to the relatively short period of time of chloramphenicol administration

It has been pointed out that depression of erythropoiesis manifested by a decrease in the reticulocyte count was the first and most frequent warning of trouble in patients receiving chloramphenicol. We could not use the reticulocyte count to detect early bone marrow toxicity due to chloramphenicol administration. This may be due to the relatively short period of time that the drug was given in our patients

Krakoff *et al.* [8] systematically studied the effects of large doses of chloramphenicol given for prolonged periods in four subjects. Reticulocytopenia developed in all subjects given 6 g per day for 10 to 12 days, In Cases 25 26 29 31 and 33 bone marrow counts done on the last day of chloramphenicol administration showed more erythroid elements than those of the counts done before the chloramphenicol administration

This indicates that chloramphenicol had no effect on the recovery phase of decreased erythropoiesis due to infection, and shows the need for bone marrow examination prior to treatment with chloramphenicol. By this means the occasional occurrence of erythroblastopenia in the course of infections, will not be attributed to chloramphenicol

Our studies suggest that when chloramphenicol has to be used it should be discontinued as soon as possible Then the incidence of bone marrow morphological abnormalities is not high and the marrow changes are reversible It is of interest that of the two patients who developed erythroid hypoplasia one of them received the drug for 20 days.

Bone marrow counts done ten days after chloramphenicol had been discontinued showed erythroid hypoplasia to be still present in Case 22 and to have occurred for the first time in Case 41 This may be due to the infection alone or to chloramphenicol or to both It is of interest that both patients had whooping-cough with superimposed infections.

Administration of chloramphenicol may occasionally be followed by suppression of thrombopoiesis and leucopoiesis. None of our patients developed leucopenia or thrombocytopenia

The main purpose of this study was to estimate the incidence of bone marrow morphological abnormalities in patients receiving chloramphenicol. We found the

ncidence was not high in patients receiving he drug in therapeutic doses and for a elatively short period of time Moreover appears that normal subjects are more uitable for morphological studies of the ffect of chloramphenicol on bone marrow han patients suffering from infections nd/or from anemia.

From the studies of Saidi *et al.* [13] it ppears that anemic patients and patients uffering from infections and receiving hloramphenicol react differently from ormal subjects. Furthermore infection lone can cause temporary erythroid ypoplasia [1].

At the present time lack of knowledge egarding the mechanism of toxicity makes it difficult to predict which pa ients will develop irreversible bone mar ow depression as a result of chloramphen col administration. A direct chemical ffect is suggested by the evidence that morphologic blood and bone marrow hanges are dependent on the amount iven [5 13]

The fact that doses of chloramphenicol hich are well tolerated by the majority f patients without demonstrable blood changes, can cause aplastic anemia in certain individuals is suggestive of a drug idiosyncracy [3]

By using therapeutic doses of this drug for a short period of time the incidence of temporary erythroid hypoplasia may be decreased. In view of possible drug idiosyncracy chloramphenicol should only be used when the potential benefits of its administration outweight the relatively small risk of developing irreversible bone marrow damage.

Summary

The bone marrow of 45 patients suffer ing from various infections and receiving chloramphenicol, was examined morphologically Infection alone depressed ery thropoiesis in 6 patients. Two patients developed depression of erythropoiesis while receiving chloramphenicol. One patient developed erythroid hypoplasia ten days after chloramphenicol had been discontinued Chloramphenicol used in therapeutic doses for a relatively short period of time is not associated with a high incidence of bone marrow morpholog ical abnormalities.

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A Bacteriological Comparison between Two Methods of Exchange Transfusion

by HANS JÖRGEN ANDERSEN and STIG E. HOLM

In an article by Holm Lind & Waldenström [3] three cases of sepsis in newborn babies after umbilical exchange transfusions were reported. As a consequence of these accidents we have at this clinic changed our technique of exchange transfusions from the usual trans-umbilical to a supra umbilical approach of the vein as described by Sanchez]. In this report we present a comparative investigation of the two methods from bacteriological point of view

M terial and Methods

The material consists f 23 newborn babies which had late exchange transfusions performed because of hemolytic disease of the н. All the patients were between and five days old.

The umbilical stump was cut close t the under sterile conditions and a swab as taken from the opening of the umbilical vein. Afterwards the umbilicus was covered ith sterile bandage and the umbilical vein was uncovered through a supraumbilical incision. Before the catheter was inserted int the vein a piece f the vein was taken for bacteriological examination.

The samples for bacteriological testing were put into Stuart transport medium and immediately sent t the laboratory for examination. The swab and the umbilical vein were cultured in beef-heart infusion broth with addition of 10% inactivated horse serum and incubated at 37°C for 5 days. Daily proofs were taken from the broth medium and inoculated on ordinary blood agar plates to ensure eventual growth. Gram-negative rods were typed by using a modification of "Bunt Reihe and staphylococci were tested for coagulase activity Coagulase positive strains were called st ph ylococcus ureus.

Results

No growth in either umbilicus or vein was found in six cases. Growth was found in the umbilicus in sixteen cases. A variety of bacterial types were isolated and no special type was found in a higher frequency In two of the sixteen cases bacteria were also found in the vein (*Staphylococcus aureus* and *E coli* respectively) In one

TABLE I. *Results f bacteriological examination in 23 babies subjected to exchange transfusions*

Growth in umbilicus	Growth in umbilical vein	No. of cases
−	−	6
	−	14
	+	2
−	+	1
	Total no. of cases	23



Fig 2. Case 1

(Fig) Her behaviour was quite normal until she was 25 hours old, when she started to have repeated clonic con ulsions with varying right and left dominance In association with the convulsions there was pronounced sweating and her face was flushed She was referred to the Children s Hospital when 28 hours old *She gave the general impression* of brain damage She was lethargic without normal spontaneous activity and the Moro reflex could not be elicited. Sparse twitchings of the extremities were noted. The anterior fontanel had a normal tension. Respiration was superficial and irregular with a rat of about 50 per minute. Her colour was slightly cyanotic. Heart action was agitated with visible pulsations in the epigastrium, heart rate varying betw een 90 and 120 per minute Auscultation of heart and lungs revealed *nothing* abnormal The liver was moderately enlarged and both kidneys were easily palpable. During the examination the child suddenly cried "cerebrally and had another attack of generalised convulsions of the type observed previously Convulsions subsided after bout 30 seconds but were repeated at irregular intervals. The occurrence of sweating and fl shing in association with the convulsions led to a tentative diagnosis f hypoglycemia [6]. The blood sugar value was found to be less than 10 *mg % (Somogyi-Nelson* method) A lumbar puncture was performed, the only abnormal finding was a low sugar alue of 8 mg %. Other laboratory data were withi normal limits xcept for a moderat acidosis with a bicarbonate value of 14 mEq/L, a serum phosphate of 9.5 mg % and a serum calcium of 8.2 mg %. The hemoglobin alue was 21 4 mg %, there were 5.7 million red and 14 000 whit blood cells wit two normoblast per 100 white cells. The *electrocardiogram was normal. Roentgen* examination of the chest showed the heart to be moderately enlarged; there were no atelectases and no pulmonary stasis.

The infant wa given glucose orally in small port ons. She did not vomit and repeated blood sugar controls showed values between 27 and 60 mg %. Mephobarbital was given in doses of 75 mg every eight hours. In spite f these therapeutic fforts the convulsions persisted though they were less frequent than before On the next day increasing signs of heart failure were noted: *cyanosis was more marked*, a soft systolic murmur wa heard over the heart, widespread fine rales over the lungs and the liver had increased in size Blood pressure (flush method) was 80 mm Hg, pulse rate had increased to between 140 and 160 per minute. An ECG showed signs of myocardial damage with a deeply negative T wave in the first lead. After withdrawal of 30 ml f blood from the umbilical vein a 5 % glucose solution with additions of hydrocortisone digitalis and teophyllamine was given intravenously During the next few hours *signs of heart failure diminished*, but despite blood sugar val es in the range f 25 mg % convulsions



Fig 3. Case 1 Section of pancreas showing conglomerate of islets of Langerhans of varying sizes.



Fig 4 Case 1 An islet of Langerhans showing nuclear polymorphism.

increased in severity and the child died at the age of 65 hours.

Pathologico-Anatomic Findings

Autopsy Increased subcutaneous fatty layer The heart weighed 30 g and had normal configuration with ordinary large vessels and coronary arteries. The lungs were collapsed and red-violet colored. Parenchymatous air spaces were found in the peripheral areas and the right middle lobe. The liver weighed 220 g and the cut-surfaces were dark reddish-brown and homogeneous throughout No changes within the abdominal organs or urogenitalia were noted. Pancreas normal. The spleen weighed 12 g The adrenals weighed 20 g and the ratio of the weight of the adrenals to that of the kidneys was 1 2.8 (normal 1 3). The thyroid gland (12 g) was markedly enlarged and had a brownish red cut-surface. The thymus weighed 21 g and was macroscopically normal. The brain weighed 300 g with no external changes nor changes on the cut-surfaces. Chemical analysis in respect to glycogen content in the liver showed normal values [11].

Microscopic findings. Myocardium No significant changes. Glycogen-staining negative. *Lungs* Extensive atelectasis. No hyaline membranes or inflammatory changes. *Liver* Moderately extensive nodular as well as diffuse extramedullar hematopoiesis, erythropoiesis dominant over myelopoiesis, no hemosiderosis. Liver cells normal. The sinusoids somewhat broadened and blood filled. No bile stasis and no deposition of fat or glycogen in the liver *Spleen.* Moderate extramedullar hematopoiesis of the same type as



Fig. 5.



Fig. 6.

Fig. 5. Case ... The central portion of lobulus which primarily consists of endocrine tissue but which also shows mixture of exocrine and endocrine tissue

Fig. 6. Case ... I connection with a detritus-filled duct proliferations of endocrine tissue with alpha as well as bet -cells are noted. Infiltration of inflammatory cells is seen within the area around the duct

that found in the liver but no hemosiderosis. *Thymus* Normal. *Kidneys* Some isolated small foci f extramedullar hematopoiesis in the cortex. The t bules cont in no glycogen. *Bra* Normal. *Thyroid* Small follicles of equal ize with med um high epithelium and with ery little colloid. Pronounced hyperemia within the parenchyma. *Adrenals.* Very small mount of lipoid material in the cortex otherwise normal. *Hypophysis* Advanced differentiation within the hypophysis with an increased number f eosinophilic and basophilic cells. *Pancreas* Exocrine tissue without change. The islets f Langerhans in several places were clearly demarcated from the exocrine tissue but here and there a mixture of the endocrine and exocrine tissue was noted. Moderate as well as pronounced nuclear and cell pol morphism observed here and there particularly within the larger islands, but no mitosis was observed. Several islands with a diameter greater than 200 µ. A differential count f alpha and beta-cells on sections impregnated with silver according to Gros-Sch ltze showed an alpha–beta ratio f 1 3.

Case

Case history The first f the diseased sisters was born t term. The mother had albuminuria with a maximal amount of 8 promille during the last month f pregnancy Blood pressure was 120/70. E egrounds were normal. Delivery was normal without signs

of intra or extrauterine anoxia. The child eighed 4960 g, measured 55 cm in length and had a head circumference f 35 cm During the first six hours there was nothing abnormal but then a slight cyanosis was observed There was no respiratory distress. When 20 hours old the child had tw attacks f cyanosis lasting a few minutes. Three hours later she was referred to the Children Hospital. She was big and fat had a weak cry was hypotonic and gave the general impression f cerebral damage. Only circum orally was there cyanosis, some petechiae were seen in her face The respiratory rat was 60 per minut without pparent distress. The pulse rat was 116 per minut Some fine rales were heard over the lungs. The laboratory studies revealed an erythremia with hemoglobin value f *6 g% and 8.1 million red blood cells. Thrombocytes amounted t 130.000 and the prothrombin index was 53. The CO_2-combining power was 24.6 mEq/L.—During the first two hours after admission the child was given oxygen and had normal colour She then had some clonic convulsions, became deeply cyanotic and suddenly died.

Pathologico-Anatomic F ndings

Autopsy N malformations. The heart weighed 29.5 g and was f normal configuration. Small petechiae were observed in the visceral pericardium. The cut-surface f the lungs was deep red and the central portions of the tissue were dry The liver weighed 270 g and had a bloody cut surface. Nothing exceptional in the bdominal organs. The pancreas weighed 2.5 g and was of normal size form and consistency The spleen weighed 14 g. Kidneys, ureters, urinary bladder and genitalia were normal. The adrenals weighed 11 g and the ratio f the weight of the adrenals to that f the kidneys was 1 4. N hemorrhage or necrosis was observed on any f the cut surfaces f the brain.

Microscopic find ngs. Lungs. Primarily centrally located atelectasis and extensive hemorrhage in the parenchyma. N hyaline membranes. *Liver:* Moderately pronounced blood stasis and ery faint extramedullary hematopoiesis. No vacuolation of the liver cells. *Brai* Markedly dilated blood filled vessels within the arachnoidea. The parenchyma without not ble changes. *Adrenals* Normal. *Pancreas.* Nothing noteworthy in the exocrine tissue. Obvious hypertrophy and hyperplasia f the endocrine tissue with an increase in the number of islands of Langerhans. The diameter of several of the islands measures 230–350 μ The endocrine tissue is most ften diffusely limited by the exocrine tissue and in several places insular tissue is observed interstitially Within the insular tissue and particularly within the larger islands a pronounced nuclear and cell polymorphism is apparent The nuclei show a variable chromatin content but no mitosis. In connection with detritus-filled duct proliferations of endocrine tissue with alpha as well as beta-cells are noted. Infiltration f inflammatory cells is seen within the area around the duct.

Discussion

Marked flushing and sweating in connection with convulsions are characteristic features of hypoglycemia but are not seen in other types of cerebral attacks [6]. No intracranial bleeding could be found in either of the two cases at autopsy The absence of respiratory distress makes it reasonable to look upon the observed pulmonary telectases as secondary mani festations. Thus hypoglycemia must be regarded as the essential cause of death in Case 1 In Case no blood sugar determination was made but the similar clinical course and pathologico-anatomic findings point to hypoglycemia as the cause of death in this child also.

The gross appearance of these patients was not distinguishable from that of an offspring of a diabetic or prediabeti mother An impaired calcium-phosphorus

homeostasis and a high hemoglobin value are common findings in these infants [1 20]. However very low blood sugar values in the range of 10 mg % are usually seen only during the first few hours of life and hypoglycemic symptoms as mentioned previously are rare at this time

The pathologico-anatomic findings were also remarkably similar to those found in an offspring of a diabetic or prediabetic mother In the present cases hypertrophy or hyperplasia of the islets of Langerhans were demonstrable in the pancreas A moderate or marked nuclear and cell poly morphism was noted in the endocrine tissue as well as a proliferation of the insular tissue Potter *et al* [16] have suggested 250 μ as the upper limit for the diameter of a normal islet In the present cases several islands with diameters of as much as 400 μ were measured According to Ferner [4] a calculation of the alpha to beta-cell ratio offers a better indication of the activity of the islands of Langerhans than an estimation of the degree of hyper trophy and hyperplasia of the islands. Terbrüggen [19] has calculated the alpha to beta-cell ratio in neonates to be 1 1.5 and approximately the same ratio has been stated by Seifert [18]. In Case 1 the alpha/beta ratio was 1 3 the same as that observed by Hultquist *et al* [10] in off spring of diabetic mothers. Thus a relative increase of insulin producing beta-cells was found in Case 1 Of importance in this connection is the fact that alpha-cells were demonstrable in both cases. McQuarrie has discussed the absence of alpha-cells as an etiological factor in neonatal hypoglycemia. He refers to a small series where hypoglycemia occurred and partial pancreatectomy was performed. Histological examination after staining according to Gomori showed a complete or almost complete lack of alpha-cells and slight granulation of the beta-cells. Familial incidence of this condition was high.

The existence of insular changes similar to those found in infants of diabetic mothers does not of course prove that these patients had the same basal metabolic disorder As mentioned before, the clinical course was different from that usually seen in offspring of diabetics The normal glucose tolerance test in the mother does not in itself exclude a prediabetic state as it is well known that diabetic women may give birth to very big infants several years before a pathologic glucose metabolism can be verified [5]. However the normal birth weight and absence of symptoms in the child born after the diseased sisters makes a diagnosis of prediabetofetopathia less probable.

Pathologico-anatomically there may be great difficulties in differentiating between foetopathia diabetica and erythroblastosis foetalis [14 17]. In the present cases the latter diagnosis might reasonably be ruled out on clinical grounds. The mother is Rh positive and there was no anemia or visible icterus in the infants.

During recent years an increasing interest in various types of hypoglycemia in infants and children has been apparent In 1954 McQuarrie [1°] related 25 cases of idiopathic spontaneously occurring hypoglycemia in infants He noted a tendency to familial occurrence Some of his cases had symptoms as early as during the first few days. Birth weights are not mentioned but "all infants were well within the normal ranges of weight and anthropometric measurements for their

s. In a later review by Haworth *et al* [9] another 76 cases are added and it is out that some of the "idiopathic" s may now be properly classified as "leucinsensitive" or as having an insufficient release of adrenalin in response to hypoglycemia. Among the cited cases in the latter review is one girl published by Gall *et al.* [7] showing some traits similar to the present cases. She weighed 4670 g at birth and was well during the first 30 hours. Thereafter she started to have convulsions. A lumbar puncture showed normal findings. Hypoglycemia was not suspected at that time but when the girl was admitted at six weeks of age because of repeated convulsions the blood sugar was found to be between 10 and 40 mg %. At eight months the child was operated on and the entire pancreas was palpated without discovery of any tumor. Biopsy of the pancreas showed histologically a normal picture. The convulsions could only be partially controlled and the child became severely mentally retarded and died at 4½ years.

Apart from the case related above we have only been able to find one earlier case in the literature resembling those herein described. In 1937 Hartmann *et al.* [8] described a girl of a healthy mother who was "large and flabby" at birth and weighed 5140 g. Delivery was normal. When two days old the girl started to have convulsions and died six hours later. The only abnormal finding at autopsy was islet hyperplasia in the pancreas and the author believed hypoglycemia to be the cause of death though unfortunately no blood sugar determination had been made.

In the present cases the rapidly fatal outcome prevented any further analysis of the cause of the hypoglycemia. The fact that the parents are first cousins gives support to the supposition that this syndrome with hypoglycemia may be genetically determined.

Summary

A clinical and pathologico-anatomic syndrome resembling that occurring in offspring of diabetic and prediabetic mothers has been described in two overweight newborn sisters. Both patients had convulsions and died during the neonatal period. In one of them where blood glucose determinations were performed a marked hypoglycemia was diagnosed.

Since the mother has given birth to quite normal infants between and after the diseased children and because of the fact that there is no evidence of a prediabetic state, it is suggested that the syndrome has developed as a consequence of some other metabolic error. The fact that the parents are first cousins supports the supposition that the disease may be genetically determined.

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The Use of an Oral Airway in the Treatment of Respiratory Distress of Infants

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The use of an oral airway in the treat ent of respiratory distress due to block ge of the nasal passage in infants, is des ribed in a series of cases which might therwise have proved fatal. This pro edure was found useful, not only in cases f congenital malformation but also in ases of acute inflammatory obstruction. t was found possible to use an oral airway or extended periods of time in order to lefer surgical reconstruction of the nose until a more suitable age.

The oral airways we have used consisted imply of a length of ordinary rubber ubing inserted into the mouth just far nough, so that the inner opening could ot be occluded and so that the tongue ould not press against the roof of the outh, thus allowing ventilation through nd around the tube It takes only a few moments to manipulate the tube into a osition which allows ventilation with no isk of inducing gagging.

There are great individual differences in he age at which the ability to breathe through he mouth is developed in infants. The ormal response f the newborn t blockage f the nasal airway is to close the mouth and ry to force ir through the nose thus causing ballooning ffect of the soft palate which pressed against the base f the tongue. During the inspiratory phase the infant presses the tongue against the roof f the mouth [4]. This process results in a struggle for ir leading to exhaustion and asphyxia. There appears t be no reflex which allows calm mouth breathing in such cases Ventila tion, however is possible through crying. In 1914 Richardson described a type f respiration in congenital choanal atresia consisting of alternate crying and pnea [16] later named cyclic dyspnea by Lebensohn [10]. The exhaustion which results from this laborious respiratory ffort leads t death just as has been described in other form f respiratory distress [7].

The onset of the ability t breathe calmly through the mouth varies widely One oc casionally sees the newborn sleeping with its mouth open but it is breathing through the nose [6]. Exhaustion and death are the usual consequences of untreated congenital bilateral total choanal atresia according to Beinfield [1]. However statistics on the subject are not available and cases f late diagnosis f the condition have been de scribed [2]. Kazanjian [8] has reported the case f a girl with this deformity who had so few symptoms that her condition was not diagnosed until the age of 15, McGovern [12] mentions another such case diagnosed at the age f 19 Her only reported symp toms were feeding difficulties as an in fant Various authors [11 13, 15, 16], suggest that the most usual age for the onset f mouth breathing bility is during the second and third weeks f life. Haenckel [3] reports case of congenital hoanal atresia in which a tracheotomy tube was inserted at

one month of age and could not be finally removed until the age of five months. Kiel [9] reported a case in which the infant died at the age of four months after recurrent attacks of dyspnea even though there were congenital perforations of the roof of the mouth. A case operated upon for choanal atresia on the second postnat l day had to have nasal t ibes nightly even at the age of 11 months, to guarantee adequat respira tion [14]. The variations in the bility to breathe through the mouth lo not seem to be related to prematurity brain damage or associated congenital defect

The infants with breathing difficulties which we have treated with oral airways (see below) were afflicted with congenital malformations or inflammatory blockage of the nasal passages. Nose drops aspira tion of secretions and antibiotics were attempted but failed to relieve the breath ing difficulties. Plastic tubes through the nose were found to be of limited value because it was necessary to use fine calibre tubes which were quickly blocked. Fur thermore they sustained mucosal inflam mation. In our hands intermittent nasal dilatation was not effective in treating cases of inflammatory stenosis Moncrieff [13] reported success with this treatment in some cases.

Case Reports

Case 1

This was a girl born 17 days before the expected date of delivery weighing 2350 g. She had neither external nose nor nasal openings, and there were also defects f the eyes, the ears, the upper lip and jaw Im mediately after birth she displayed respiratory distress, asphyxia and cyclic dyspnea, as described bove Her mouth had to be kept open manually in rder t allow her to breathe

X-ray examination the day after birth showed an underdeveloped maxilla and no visualization of a nasal cavity During this day she had repeated attacks of asphyxia and apnea when her mouth was not kept open. On the third day of lif an oral firway was introduced (see Fig. 1) which consisted of a piece of rubber tubing, through which stomach t be was passed for feeding pur poses. Her attacks of respiratory distress stopped immediately and upon the re commendation of E.N T specialists it was decided to attempt to postpone surgery to a more suit ble ge During the first few weeks f treatment she tended to accumulate viscous mucus in the mouth. She was treated continuously for 3½ months with the artificial oral airway During that time she doubled her birth w ght and developed no respir atory infections, or lesions from the tubes. She had no attacks of respiratory distress except when the oral tube wa withdrawn in order to test her mouth breathing ability At the age of 3½ months she was sent t the plastic surgery unit

Case 2

This was a girl born at the expected dat in a normal manner but weighing only 2300 g. During her first week of life she developed a systolic heart murmur She had to be fed through a stomach t be At the age of one week she developed nasal congestion which resulted in partial blockage of the nose The respiratory distress was not relieved by nose drops and suction. She had limited air passage through the nose but had not the strength to maintain the effort required to force air through it On the other hand she was not able to develop satisfactory mouth breathing An oral airway was in troduced the respiration improved immed iately and her distress disappeared. Two days later after the acute nasal swelling had subsided, it was possible t remove the tube Later on it was confirmed that she suffered from a congenital malformation of the heart.

Case 3

This was a male twin with birthweight of 17?0 g and born four weeks before the



Fig 1 The photos demonstrat the pplication of the tube in Case 1 Below is the tube and its cross-section.

xpected date of delivery H had to be fed hrough a stomach t be as he w very weak, ut he had no immediat postnatal asphyxia. n the tw lfth day f lif he developed hinorrhea and the nose was blocked, which d to respiratory distress and cyclic dyspnea. uction f the nose and nose drops were effective and his fight for air was exhaust him. After an oral tube was inserted the espiration immediately improved and he ecame more calm. On the following day his was less congested and the oral t be ld be withdrawn.

At the age f 1½ months and weight f 440 g he again developed rhinorrhea nasal ongestion and respiratory distress. H had ery in order t ventilat his lungs but at this time nasal suction and nose drops were sufficient t clear the air passages. H soon recovered and had no further attacks.

Case 4

This wa boy with normal, full term, spontaneou delivery and a birthweight of 2920 g. Since birth, however the patient suffered from respiratory distress. H was transferred to our hospital the day fter birth with diagnosis f massive pulmonary telectas H showed cyanosis, muscular hypotonia, cyclic dyspnea and had weak respiratory sounds over both lung fields Thin plastic t bes were inserted through the nose with great difficulty His nasal passages were narrow and no ir could pass through.

An oral tube was inserted and his respiratory distress diminished momentarily and his colour became rosy. Normal chest sounds were then observed. On the following day the oral tube was withdrawn but he developed *renewed dyspnea and the tube had to be* replaced, whereupon he promptly recovered. By the time he was twelve days old it was possible to remove the tube. He was then able to breathe calmly through his nose. Five days later he was able to drink *from a bottle*. E.N.T. consultants found narrow nasal passages bilaterally with the inferior conchae partially occluding the airway. During the second month of life he developed rhinorrhea, and his nasal passages were blocked. His breathing became distressed but he was able to develop mouth-breathing and no oral tube had to be employed. His nasal blockage was soon overcome and his subsequent stay at the hospital was uneventful.

Case 5

This was a boy born by breech delivery one month before the expected date of confinement, weighing 1770 g. He was in good condition with no breathing disturbances. When he was two weeks old he contracted rhinitis followed by blockage of the nose, respiratory distress and cyclic dyspnea. Suction of the nose and nose drops were ineffective in clearing a nasal air passage and therefore an oral tube was inserted which gave him immediate relief. The following day the acute swelling had subsided enough to allow nose breathing and the tube could be removed. Two days later the nose was blocked again and the cyclic dyspnea returned. The oral tube was put into place again with the same good result and could this time be taken away after a couple of hours when suction and nose drops had managed to clear the nasal passages.

Case 6

This was a boy born in breech position one and a half months before the expected date of delivery and weighing 1600 g. He had an attack of asphyxia immediately after birth, and during the first two weeks of life he showed sternal retractions with each respiratory movement. He had good breath sounds and no râles. When he was one and a half *months* old he developed nasal congestion followed by cyclic dyspnea and *cyanosis. An oral tube* was put into place and his respiratory distress disappeared and the colour returned to normal. After a few hours treatment with nose drops and nasal suction he was able to breathe through the nose and it was possible to remove the tube. His further course was uneventful.

Case 7

This was a girl born three weeks before the expected date of delivery weighing *1870 g*. She was in good condition. When she was one week old she developed nasal congestion followed by respiratory distress. An oral tube was introduced and her cyclic dyspnea and cyanosis disappeared. The tube could be withdrawn on the following day when nose drops and nasal suction were sufficient to clear the nasal passages. She could later be discharged in good condition.

Discussion

It has been seen that children with a birth weight of less than 2000 g even without nasal anatomic defects may develop an inflammatory blockage of the nose resulting in an acute fatal dyspnea. This occurs during the first 2–3 weeks of life, while the child is not sufficiently mature to breathe calmly through the mouth. The degree of nasal blockage is the critical factor involved in this dyspnea. We have seen children in poor general condition and weighing less than *2000 g* who developed acute rhinitis with only partial nasal blockage and they managed to maintain satisfactory nasal respiration and required no oral airway. However *children in this weight group* are more liable to develop a total nasal blockage when they contract an early rhinitis. In

series of cases every one of those ildren weighing less than 2000 g at rth with a complete nasal blockage ing the first three weeks of life re ured an oral airway for respiration be- use they were not able to develop tisfactory mouth breathing. It is our nion that these children would have n a considerable risk of dying from haustion and asphyxia if they had not ad the benefit of such treatment

In our experience children with a birth eight of over 2000 g developing an early ainitis have been able to maintain a n degree of nose-breathing with the d of conventional therapy But in Case 2 was still necessary to use an oral airway ecause of the poor cardiac condition, the bour required to force air through the ose could not be maintained. This case xamplifies how a partial blockage of the ose can be a fatal situation in a child of r general condition who is unable to tunt over to calm mouth breathing nd that an oral airway may be effective such cases. The use of an oral airway in ses of dyspnea caused by congenital cclusion of the nose was found to be hly satisfactory

We have found treatment with an al airway unexpectedly free from com lications. Not a single accident due to aspiration occurred. The oral airway may be used for months without complicating infections of the pharynx, bronchi or lungs. This was rather unexpected since mouth breathing dries the mucous membranes, increases the viscosity of secretions and increases the risk of infection, particularly in the subglottic space [5 17] It may be that the airway functions as a heat and moisture exchanger so that part of the water content of the expired air condenses in the tube and then evaporates during the following inspiration [17] Th irway also diminishes the necessity for frequent nasal suctioning which perpetuates in flammation. Although there were super ficial skin lesions from the adhesive tape fastening the tube there were no mouth lesions from the tubing

Summary

Fatal respiratory distress in children with a birth weight below *000 g brought about by rhinitis within the first two to three weeks of life and in children with congenital nasal defects, has been treated with a simple mouth tube This was found to overcome the children s inability to breathe through the mouth, thus relieving their exhausting respiratory efforts without causing any serious complications even when used for periods of months.

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CASE REPORT

Pure Red Cell Anemia in Step Siblings

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Hypoplastic anemia of the Blackfan Diamond type ("pure red cell anemia") is a well defined disease entity. More than hundred cases have been described in the literature [3–5, 7–14]. Out of these only a few have been familial in two pairs of brothers [.., 9]. Nevertheless several characteristics favour the assumption of a genetic origin: early onset, signs of disturbed tryptophan metabolism, over-representation of associated anomalies etc. [6, 1].

In the following a short report will be given of two children who both manifested the typical disease picture. The children had the same father but different mothers.

Case Histories

Case 1

G.W., a girl, was born March 29, 1938. She has been reported twice in earlier publications [10, 14]. From the age of three years the anemia gradually became stabilized. In years the hemoglobin values have been around 6–9 g%.

Case 2

J.L., a boy, was born April 3, 1951. He is the second of four legitimate children. [illegible] appeared in the first few months of life and from 4 months he has been treated regularly with blood transfusions at intervals of 1 months. From the age of 4 he has shown signs of increasing hemosiderosis with hepatomegaly and also skin pigmentation. Treatment with ACTH in small dosage (5 IU/day) was without effect at the age of 2½ years. Later on, at 5½ years, Prednisone 5–10 mg/day for 5 months had no effect. With a considerably higher dosage (40 mg/day for a week) at the age of 6 years temporary remission was induced.

At the age of 11 years the boy is still in need of transfusion therapy and has so far obtained 182 transfusions with a total amount of 48 100 ml blood.

It has been established that Case 2 is step-brother of Case 1. The pedigree is given in Fig. 1.

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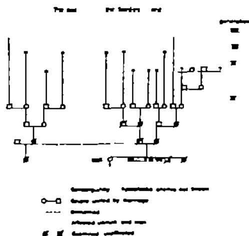


Fig. 1

Discussion

The two cases of "pure red cell anemia" here described manifest the classical, clinical picture. They deserve a special interest only because of their kinship. Since the father was the same for both patients it is reasonable to assume that the disease is under genetic control and that the father is carrier of a dominant gene with reduced expressivity. A similar hereditary pattern of this disease has not been previously described. There was no consanguinity in the families and no other cases of the disease under discussion were known.

Summary

Genetic evaluation of two step siblings with "pure red cell anemia" favours the assumption of a dominant gene with reduced expressivity as a cause of the disease.

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CASE REPORT

Diencephalic Syndrome of Emaciation

Report of a Case

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In 1951 Russell described a diencephalic syndrome of emaciation" occurring in 5 children [7], and in 1957 he presented additional cases [8]. The cardinal features, presenting in infancy or early childhood, were profound emaciation in spite of normal appetite and normal calorie intake linked with an almost paradoxical locomotor over-activity with signs of euphoria. In all instances ventriculography, craniotomy and/or necropsy ...ed tumours in the hypothalamic ...on.

Similar cases have recently been re...ed by Dods [3], Hagan [5], Braun et al. [2] and Marie et al. [6]. The purpose of the present paper is to report an additional case of this syndrome.

Case Report

The patient, a boy, was born on January 3rd, 1961 to unrelated and healthy parents. ... father had been extraordinarily thin during infancy but later showed normal growth and weight gain. Congenital anomalies or metabolic disturbances have not been observed in the family. Eight older siblings are normal and healthy. The pregnancy was uncomplicated until the seventh month. The mother then suffered from a heavy uterine hemorrhage necessitating hospitalization and blood transfusions. The patient was delivered 2 weeks before estimated term. The delivery was uneventful. Birth weight 3270 g, height 50 cm. The neonatal period was completely normal. He was nursed for 2 months and later bottle fed on prescribed formula. For the first 2 months he showed normal psychomotor development and seemed to gain normally. He was not weighed regularly, however. When he was 2 months old he started to vomit and from then on did not gain satisfactorily. At the same time his parents noticed peculiar jerking eye movements.

When five months old he was admitted to the local hospital. He was then extremely emaciated weighing only 4360 g. He was pale. A constant nystagmus was noted. Because he had been exposed to varicella he was discharged after a few days and was readmitted when 8 months old. He was then almost like a skeleton, his height 67 cm and his weight 4500 g. Nystagmus, pallor and slight brownish pigmentation of the skin and hyperextensibility of the finger joints were noted. Blood analyses and estimations of the excretion of 17-hydroxycorticosteroids in the urine showed normal values. In spite of normal appetite and high calorie intake the patient failed to gain and was then transferred to the University Pediatric Clinic, Rikshospitalet. He was then 9½ months old. The emaciation was extreme



Fig. 1

with almost complet loss of subcutaneous fat (Fig. 1). His height was 68 cm (‹5 per centile for his age). His weight was 4290 g which is 1600 g below the ‹5 percentile for his height. Head circumference was normal, 43.5 cm. The anterior fontanel measured 2 1.5 cm and the tension seemed normal. He was very pale and there wa a slight greyish-brownish discoloration of the skin. He sweated easily. There was marked general hypotonia with hyperextensibility of the finger and toe joints, and a slight hypotrophia of the skeletal muscles. Motor function was retarded. H was not able t sit without being held firmly and he balanced his head with difficulty. Contrasting with his extreme emaciation he showed a remarkable hyperactivity his arms and legs being almost constantly in eager movements except during sleep. H was also paradoxically alert and good humoured, eagerly seeking contact and easily made t laugh. There was a constant horizontal undulating nystagmus. The ophthalmologists also suspected that he suffered from leftsided abducens paresis and a probable leftsided homonymous hemianop a. Except for this, neurological examination revealed nothing abnormal. Papilledema was not present on several repeated examinations. Blood pressure was normal. His penis was slightly enlarged. Both his testes were descended.

Laboratory investigations

The results of the blood analyses were within normal limits.

Oral glucose tolerance test with 8.4 g glucose in 25 ml of water showed flat curve. The fasting level was 72 mg/100 ml, the maximum reached after 60 and 90 minutes was 79 mg/100 ml and the lowest level reached 2 hours after the oral load was 75 mg/100 ml.

Urine analyses were normal. Urine chloride 150 mEq/l. Urinary excretion of 17-hydroxycorticosteroids 0.4–0.7 mg/day of FSH 8 MU/day of luteinizing hormone 4 MU/day of androsterone 0.2 mg/day of dehydro-

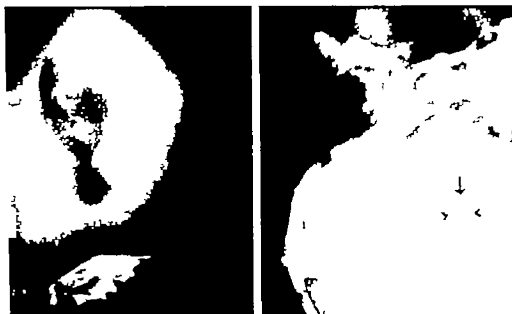


Fig. 2. Pneumoencephalograms showing filling of the dilated left lateral ventricle (no filling of the right one). The third ventricle is displaced in an upward direction, the floor of the ventricle only 7 mm from Foramen Monroi (> <). There is convex impression int the floor of the third ventricle (arrow).

epiandrosterone 0.1 mg/day and f etiocholanolon 0.2 mg/day. Following a methopiron load (250 mg) the urinary excretion of 17 hydroxycorticosteroids increased from 0.4 mg/day t 1.6 mg/day (normal). Paper chromatography of the urine showed normal amino acid excretion pattern. His spinal fluid contained 198 mg/100 ml f protein and 4 mononuclea cells per mm³. Bacterial cultures from blood, spinal fluid and urine were negative. The stools were f normal color and consistency and cont ined normal amounts of fat and protein on microscopic examinations and quantitat ve analyses.

X-ray f the skull and long bones were normal. The skeletal maturation was slightly retarded but within normal limits. The EEGs showed patterns within normal limits. The electromyogram was normal. Two unsuccessful ttempts were made t perform a pneumoencephalography by the lumbar rout It was then decided t perform a direct ventriculography but this had t be postponed because of intercurrent respiratory infections. In the meantime the patient seemed t lose much of his activity and lost his appetit as well. His alertness and locomotor act vity decreased, and arm and leg movements ppeared more thetoid. The nystagmus persisted. There was no papill edema. The head circumference was unchanged. The ir ventriculography was performed in the neurosurgical department. The X-rays (Fig. 2) demonstrated internal hydrocephalus and a convex impression into the floor f the third ventricle. This was displaced upward t about 7 mm from foramen Monroi. Expansive process in the third ventricle was considered probable.

The neurosurgeons considered the tumour inoperable and the patient was transferred t the local hospital. A f tal outcome must be anticipated.

Discussion

The characteristic features of the diencephalic syndrome of hyperkinetic emaciation as described by Russell and others are as follows.

There is a profound emaciation presenting in infancy or early childhood in spite of normal or enhanced appetite and adequate caloric intake. The patients exhibit "hyperkinetic vivacity eager over-alertness, indiscriminate over friendliness and predominant elation" as originally stated by Russell [8]. Pallor of the skin is often prominent though anemia is usually not present. Excessive sweating especially of the head and face, has been reported repeatedly An initial growth spurt was reported by Russell [8] but has not been a constant finding Russell also reported the occurrence of hypoglycemia in some *of his patients.* Some of the patients had periods of vomiting Nystagmus is often observed Neurological signs of cerebral involvement other than nystagmoid eye movements are very rare and usually present themselves late

Hypothalamic neoplasms have been established as the common pathological basis of the syndrome Craniotomy or necropsy have almost invariably demonstrated astrocytomas. Russel originally attributed the emaciation to a disproportionally increased energy output resulting from increased basal metabolism and the locomotor hyperactivity More recently it is suggested however that at least some of the symptoms may be caused by direct influence of the tumour on the hypothalamus [5 6]. Animal experiments [1] as well as clinical case reports [4] have demonstrated that lesions in the hypothalamic region influence the appetite and according to Russell [7] interruption of the fronto-thalamo-hypothalamic circuit or lesions in the dorsomedial thalamic nuclei produce loss of the natural shyness and hostility in experimental animals. Skin pallor sweating, vomiting etc. may be *autonomic symptoms* secondary to a hypothalamic lesion. Nystagmus may be caused by impairment of vision due to compression of the chiasma but also may have a more central origin.

In patients with symptoms and signs resembling those described, hypothalamic lesions should be suspected. Pneumoencephalography is a very important diagnostic procedure and may reveal a tumour Astrocytomas in the hypothalamic *region are usually not satisfactorily treated* surgically and these neoplasms are relatively resistant to radiation therapy However early diagnosis and intervention may perhaps save some of these patients.

Summary

A new case with diencephalic *syndrome* of emaciation is reported The first *symptoms* occurred when the patient was 2 months old. Ventriculography demonstrated a probable tumour in the third ventricle The patient is described and the findings shortly commented on

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CASE REPORT

Generalized Cytomegalic Inclusion Disease in a Newborn Infant

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Although generalized cytomegalic inclusion disease in the new born is recognized with increasing frequency it is still a rare condition. The literature however on this subject has become extensive especially during the last ten years, with contributions from almost every part of the world. This great interest has been very rewarding as the condition during the last decade has emerged from the pathologist's domain to the field of the clinician.

Prior to 1952 the disease was diagnosed exclusively at autopsy. Wyatt *et al.* [19] in 1950 were the first to point out that it might be possible to diagnose cytomegalic inclusion body disease intra vitam by demonstration of the typical cells in urinary sediment. Fetterman [6] in 195 and Mercer *et al.* [13] in 1953 succeeded in doing so. The latter also defined the clinical picture of the disease in the new born. In 1955 Margilith [11] was the first to report a case of a patient who survived after treatment with cortisone. Two years later McElfresh *et al.* [1] reported two patients who survived without treatment, but, however, who suffered cerebral damage. In 1956 Smith [16] proved the viral etiology of the disease and Weller *et al.* [18] the following year were able to demonstrate the presence of antibodies against salivary gland virus, which is thought to be the responsible agent.

In Scandinavia the disease was first described from Finland [1] in 1952 (five cases) later from Sweden [3] in 1959 (one case) and from Norway [7] in 1961 (one case). In all these cases the diagnosis was made post mortem although the disease was suspected clinically in several cases.

This paper reports the first patient with cytomegalic inclusion disease in the new born from Scandinavia, in whom the diagnosis has been made intra vitam and who has survived.

Case Report

L.B.H., a boy, was born on August 1 1960. He was the first child of healthy parents. During pregnancy the mother suffered from an urinary infection which was treated with achromycin. Otherwise the pregnancy was uneventful. An uncomplicated delivery took place five weeks prior to term. The birth weight was 2000 g, the birth length 44 cm. When the patient was ten days old, he started to bleed from the umbilicus, necessitating his admission to the pediatric service of the local hospital on August 28 1960. The following main data have been obtained from the hospital records. On admission the patient was in good general condition. He was moderately jaundiced and had a slight bleeding from the umbilicus. Several pustules were noticed on the neck and around the umbilicus. The head circumference measured 28 cm; the liver and spleen were grossly enlarged. Ophthalmoscopic examination revealed a



Fig 1

retinal hemorrhage of the left eye Ordinary urine examination did not show any abnormalities. Hemoglobin was 84 % the white cell count was 16 600 per mm³ with many immature granulocytes, the plat let count wa 106,000 per mm³ The prothrombin time was 66 and his blood type 0 Rh positive (the same his mother) Bleeding and lotting time were normal, while the tourniquet test was positive Osmotic frag lity f the erythrocytes was normal. Wassermann reaction, D₃ test and direct Coombs test were all negative The bone-marrow revealed hyperactive hematopoietic tissue X-ra examination f the skull and the long bones show ed no pathological find ings.

During the following weeks the hemoglobin dropped t 43 . The jaundice decreased slowly and was hardly visible in the middle of October 1960 From this time recurrent petechiae were noticed on the face neck, and trunk. Hepatosplenomegaly remained unchanged. In spite of these alarm ing findings the patient general condition was satisfactory all the time He was breast fed and gained weight The disease was treated as a septicemia, and the patient received several antibiotics and two blood transfusions.

After discharge on October 28, 1960 he was re-examined on two occasions. The petechial bleedings and the hepatosplenomegaly persisted; therefore the patient wa referred t the Pediatric Department Uni ersity Hospital, Bergen, for further diagnos tic studies. When the patient was first seen on January 19 1961 he was five months old (Fig. 1). H ppeared microcephalic his head ircumference measured 36 cm. Weight and length were within normal limits, con sidering his premature birth. The skin wa covered with numerous petechiae the liver and spleen were grossly enlarged. Ophthal moscopic examination showed no bnormal lities. The deep tendon reflexes seemed hyperactive and his motor development was retarded. Several plat let count revealed a thrombocytopenia between 50 000–100 000 platelets per mm³ Prothrombin time bleed ing and clotting time were normal. Thymol turbidity was 9.8 units. The pinal fluid was lear with no cell and a total protein content f 35 mg/100 ml. X-ray f the skull revealed a microcephalic calvarium. Intracranial calcifications could not be demonstrated. An EEG showed markedly bnormal tracings Repeated examinations of *urinary sed ment* disclosed on one occasion an enlarged tubulus-cell which contained intra uclear inclusions. This cell, however was not very well preserved and no definit conclusion could be drawn. Inclusion cells were not found in the spinal fluid. *Biopsy from the parotid gland* showed several large cell with intranuclear inclusions. A liver biopsy revealed fibrotic hanges. Cyto-

megalia or intranuclear inclusions could not be seen. The serum was tested for antibodies against sal vary gland virus. A *complement fixation antibody titer* of 1 64 was established.

The patient was re-admitted in October 1961 for a follow up examination. He was then *fourteen* months old. His mental and motor development appeared markedly retarded. He was not able to sit alone nor hold up his head while in prone position. The extremities revealed spasticity with hyper active deep tendon reflexes. The skin was still covered with petechiae The head circumference wa 41 cm (normal: 47 cm) Ophthalmoscopy revealed a normal fundus. The liver was no longer palpable; the en largement f the spleen, however was unchanged. The thrombocytopenia per sisted with a plat let count of 68,000 per mm³ X ray of the skull revealed no evidence *of intracranial calcification*, and the EEG still showed very pathological tracings.

Comment

The diagnosis in the present case is primarily based on the clinical picture Blood incompatibility toxoplasmosis, septicemia, and syphilis have been ex cluded. The diagnosis is supported by the demonstration of typical inclusion-bearing cells *in the* parotid gland and a positive antibody titer

The presence of cytomegalia and intranuclear inclusions in the parotid gland, however is not of diagnostic significance. The typical cells have been found in the salivary glands of 10 to 30 % of infants coming to autopsy [5] General involvement should be looked for Thus, the evidence of intranuclear inclusion bearing cells in the urine, spinal fluid, gastric washings, or in biopsies from other organs than the parotid gland, will establish the diagnosis. Failure to establish the presence of the cells *in* this *way however* does not rule out the diagnosis. Such cells have been found in the urines of only 50 % of neonatal cases with proved viruria [8].

The serologic tests should be used *judiciously A* negative antibody titer is found very often in cytomegalic cases, and a positive result only means a past infection. It has been shown that specific antibodies appear in the blood of 81 % of the general population over 35 years of age, with smaller proportions in younger persons [15] Rowe believes that the best time for using serology as a diagnostic tool is about the age of five months. Few normal infants have yet acquired a subclinical infection at this age and most of the newborn cases have had sufficient time to develop antibodies by this age [14]. The most reliable diagnostic test is isolation of virus from the urine. However, only a few laboratories are at present able to carry out this kind of work. It appears from the above considerations that in many cases the intra vitam diagnosis can only be made by the clinical picture and per exclusionem.

The disease is usually fatal However early *recognition of* the condition is important since early treatment with corticosteroids seems to improve the poor outlook. Katz & Kibrick [9] state that there is no evidence of the efficacy with corticosteroid treatment *in this* disease This certainly is no proof but the follow ing observations indicate that treatment with corticosteroids may be of value The few patients who have survived the disease without sequelae have all been treated with corticosteroids [2, 4 10 17]. One surviving patient with cerebral sequelae the case of Margileth [11] received treat ment with cortisone. These sequelae however seemed to be due to a cerebral

hemorrhage in the neonatal period and not due to viral involvement of the brain. Patients who have survived the disease without corticosteroid treatment have shown more or less severe sequelae. Complete spontaneous recovery has to the knowledge of the author as yet not been reported.

In the present case the diagnosis was made too late: the patient was five months old and cerebral damage was evident. Treatment with corticosteroids was therefore not indicated.

Summary

A case of generalized inclusion body disease in a newborn premature male infant is reported. The diagnosis is based on the clinical picture, the demonstration of typical cells in a biopsy from the parotid gland, and a positive antibody titer against salivary gland virus. This is the first patient from Scandinavia in whom the diagnosis has been made intra vitam and who has survived, although with cerebral damage. Several diagnostic features are discussed. Early treatment with corticosteroids is recommended.

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CASE REPORT

Development of Paraplegia after Breech Presentation

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Lesions of the spinal cord ascribable to birth traumata, in particular seen after breech delivery, have been the object of investigation, especially since 1920. In 1925 Ford [4] reported 6 cases of transversal lesions of the spinal cord, and in 1927 Crothers & Putnam [2] described in detail 28 cases and reviewed the literature on cases communicated during the period from 1870 up to the present time, viz. 20 cases, 10 of which included autopsy records.

Most of the text books are prone to refer to these ancient investigations exclusively, publications from recent years being rare, probably because podalic version no longer is used as frequently as has hitherto been the case. However, in 1959 Crothers & Paine [1] stated that "paralysis due to injury of the upper cord and lower brain stem though not common is important".

We have had the opportunity of examining a case of this nature in which severe changes developed although the trauma presumably was small; the clinical as well as the pathological findings will be briefly discussed.

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Case History

The patient, a boy, was born in 1960.

Family history. The parents were young and healthy; they had two older children. A sister had been an outpatient in the Orthopedic Hospital where she was examined for a mild hypotonic spastic tetraplegia involving cranial scoliosis. In recent years planipes had been the only remaining symptom. EEG showed normal findings.

Pregnancy had been normal and delivery took place at the stipulated time as a breech presentation. According to the midwife and the obstetrician, delivery had been uncomplicated.

Weight at birth, 3100 g, length 51 cm. For the first two days the infant had been tired and pathetic, refusing to suck. On the second postnatal day a faint jaundice developed. Edemas occurred, and the boy became increasingly dull; on the fifth day therefore he was referred to the Pediatric Department of Rigshospitalet.

On admission the boy was pathetic and lethargic. The most conspicuous symptom was slow and troubled respiration which eventually became abdominal in character involving the use of the accessory respiratory muscles and followed by cyanosis. Universal hypertonia was present. Plantar reflexes were seen after plantar irritation. Within a few days the arms were almost rigid.

In less than two weeks Moro's reflex and the grasping reflex disappeared but sucking

reflexes and primary walking reflexes persisted. The paradoxical respiratory movements continued for a couple of weeks.

Less than one month after birth mobility of the legs improved and the hypertonia became less marked. When the boy was hanging in his arms the legs would remain in a flexed position. At this stage he would occasionally run a temperature of 40°C and above, the origin of which remains obscure. He would often be in an opisthotonic position. The bladder might be palpable above the symphysis, and the urine was excreted only upon pressure applied to the lower abdomen.

When the boy was two months old he was found usually with elbows bent and dorsally reflected wrists, the legs remaining in a normal position presenting no contractions. Bilateral patellar reflexes could be evoked from the entire tibia. No definite Babinski phenomenon was demonstrable; the muscle tone of the legs was slightly reduced.

Within the third and fourth month of life his respiration improved to a certain degree although it still remained of an abdominal character. The febrile episodes continued to occur and occasionally an extravasation of urine was noted. At this stage a bilateral Babinski phenomenon was present.

The condition of the patient obviously being stationary, he was discharged 5½ months old. Five days later he was readmitted because of a respiratory infection. The following therapy was instituted: suction, administration of antibiotics and high doses of steroid agents, together with oxygen supplies. Twenty four hours after admission tracheotomy was performed followed by manual ventilation for twenty hours. Throughout hospitalization his respiration remained insufficient, generally of an abdominal character. In our opinion the respiratory muscles seemed to be paralysed. Episodes of edema, cyanosis, and fever alternated. The hypotonicity of the legs had increased. Occasionally he was found to respond to infections. The tentative diagnosis was: myelodysplasia of unknown origin (congenital? vascular?). Death occurred seven months after birth.

A great number of examinations were performed including radiological examination of the cervical spine by which normal conditions were found. After pneumoencephalography by lumbar puncture surface air was found to be present over one of the hemispheres. Repeated encephalography failed to fill the ventricular system. Ventriculography first by percutaneous puncture of the fontanelle, later by occipital puncture demonstrated the presence of symmetrical ventricles (ratio: 0.29. 3rd ventricle 3–4 mm). No effusion was found by puncture of the dura mater. The ventricular fluid contained 58 mg % of protein. The encephalographies were performed at the Neuro-Surgical Department of Rigshospitalet.

EEG was made on three occasions; a slightly abnormal curve marked by low frequency activity was found only at the second examination.

Urography and cystoscopy showed hydroureteres and trabeculation of the bladder. Urinalysis: varying degrees of pyuria and albuminuria were present; examination for amino-acid showed a presence of moderate quantities of cystine; the pattern of the amino-acids in the urine was not definitely abnormal.

The micro-sedimentation rate was increased, the maximum level being 25 mm. Complement fixation reaction and dye-test for toxoplasmosis were negative. Normal protein bound iodine, serum-calcium, serum-phosphate and alkaline phosphatase. Serum-protein: slightly reduced values with normal relative distribution apart from a certain rise in the alpha$_2$ fraction. No incompatibility of blood was observed.

Pathological-anatomical findings

The autopsy findings included the presence of dispersed pneumoatelectases and abnormally large ureters. Inspection of the brain revealed no cerebral anomalies, vessels and membranes being normal.

Cutting of the dura mater round the spinal cord disclosed a tapering area, about 15 to



g. 1 Brain and spinal cord (ventral view). The rrow marks the tapering necrotic area of the cervico-thoracic transition of the cord.

0 mm long, at the site of transition of the ervical and the thoracic segments where the embranes had thickened, fused, and be ome discoloured into a greyish tone (Fig 1) he external surface of the dura mater owever remained smooth and white; no raumatic changes of the spinal vertebrae and ligaments were demonstrable Coronal sections of the fixed brain revealed normal development without entricular dilatation and degenerative phenomena. Only the ight and left precentral gyri presented focal changes localized peripherally in the cortex. These changes included 3 t 4 striated, radially arranged processes which were characterized by a brownish colour and a red ced consistency

Horizontal sections of the spinal cord t the site of the tapering rea showed a softness of tissue which was w thout the normal pattern although the continuity remained int ct. N vascula hanges were found.

Histological examination

In addition to the telectases in the pulmonary tissue diffuse pneumonia are found. The renal parenchyma normal.

Among the specimens obtained from the brain only those from the motor cortex present pathological changes, viz. small areas f reticular structure with scarce accumulations f phagocytes rich in lipid and blood pigment. Nerve cells have dis-



ig. 2. The border of one of he scars in the motor cort At the top reticular tissue ith hagocytes containing lipids. Below gliosis with strands of astrocytes presumably proliferating. N nerv cells are seen. Hematoxylin-eosin stain. 100.



Fig. 3. Transversal section from the t pering area of the spinal cord. Dense fibrosis of the leptomeninges. Incomplete necrosis and gliosis of white and gray substance. The central canal and the anterior spinal artery are intact. Van Gieson stain. 6.



Fig. 4. Meninges and lateral funiculus at the damaged area of the spinal cord. T the left the thickened leptomeninges. In the middle necrosed white substance with invading fibroblasts and vessels. T the right gliosis. Hematoxylin-eosin stain. 100

J and astrocyte proliferation, oc lly profuse is seen. At the site f me processes the leptomeninges contain ated phagocytes containing blood pig (Fig. 3).

Slides from the spinal cord at the alt of tapering area present complet demyelina n and bsence of normal nerve cells (Fig). The tissue contains numerous small ts and many astrocytes occasionally form g dense cicatricial tissue (Fig 4). The sue encircling the central canal and an a covering one of the lateral funiculi and adjacent part of the anterior column is damaged, being without cysts but con tining isolated, severely degenerated nerve fib. Microglia is absent. The leptomeninges, hich have fused with the dura mater have anged into a dense collagen tissue ex nding as fine strands into the posterior and teral funiculi. The gliosis in the spinal rd tissue however is more pronounced an the f brosis.

Slides from the spinal cord rostral t the sion show demyelination in the posterior niculus, and slides from the lower thoracic l lumbal segments show demyelination in lateral and anterior funiculi. Apart from se degenerations, characteristic of trans rsal section, a faint demyelination of the idal tracts is seen in the lateral funiculi bove the lesion (Fig 5).

Discussion

The changes found in the spinal cord of the same nature as the ones known m contusions caused by closed, spinal jury which may be due even to traumata flicted on sites t some distance from the on. Falling down head first, and falling the buttocks may result in spinal s, the latter rather surprisingly furing even the upper thoracic segments). In all lesions of the spinal cord in- cted during breech presentation re- ted in the literature a complet trans- l lesion has been found This applies

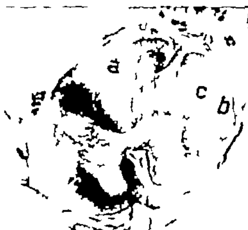


Fig 5. Transversal section from 3rd cervical segment Ascending degeneration with complet demyelination of fasciculus gracilis nd the medial part of fasciculus cuneatus ( ).Ascending degeneration with incomplet demyelination of the lateral funiculi including the spinocerebellar spinotectal and spinothalamic tracts (b), as well as descending degeneration with incomplet demyelination of the corticospinal tracts (c) Mahon myelin stain 8.

to the numerous clinical findings as well as to the less numerous pathological-ana tomical observations [5].

Direct impression of bone fragments and protruding discs exclusive the mechanism f injury may be f two types viz. ruptures f vessels along the radices followed by epidural and subdural hemorrhages and subsequent compression f the spinal cord by the hematoma [4]; one or several, minor hemorrhages in the tissue f the spinal cord ften originating from small vessels parallel t the lateral border f the grey matter [7]. Such hemorrhages are followed by necrosis extending beyond the hematoma, resorption, and fmall fibrosis or gliosis. In case f complet necrosis the final stage will be seen as a f brous scar since f broblasts will invade from the membranes; otherwise remnant f normal glia, if any may proli ferat the final stage being a glial cicatrix [6]. Such proliferation may explain the periodical clinical progression observed in our patient

The processes found in the motor cortex were identical with the ones seen in cases examined some months after birth traumata of the brain. On the basis of the morphological findings it may be concluded that the cortical processes were due to small hemorrhages the isolated occurrence suggests that the hemorrhage was of a traumatic rather than an anoxic nature. The lesions can hardly be ascribable to the *pneumo-encephalography* As already mentioned, gliosis was marked and probably it was of a progressive character both in the cortex and in the spinal cord.

The clinical findings were the same as the findings seen after the so-called spinal shock. The rigidity of the upper extremities was due probably to the cortical lesion, it was not identical with the arm lesion generally seen after avulsions of the brachial plexus.

The present case history has been reported to emphasize the urgency of including examination of the spinal cord in the necropsy of cases presenting paraplegia, but also of cases in which the neurological findings in the upper and the lower extremities are incongruous, as in the present case.

Summary

A case history of a boy born in breech presentation is reported together with the *autopsy findings*. In this case parturition had been uncomplicated. Throughout his seven months of life the boy had been marked by hypotonia of the lower extremities and of respiratory insufficiency At autopsy a closed, almost transversal lesion of the cervical spinal cord was demonstrated, including progressive degenerative processes and minor cortical injuries, all of which have probably developed simultaneously The great value of a pathological-anatomical examination of the spinal cord is emphasized.

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CASE REPORT

Chromosomal Translocation in a Mentally Deficient Child with Cryptorchidism

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Introduction

In this paper we present a case of a le child with severe mental and physal retardation, obesity and cryptor hidism in whom cytological studies evealed a chromosomal aberration inolving the large acrocentric chromosomes 4 14, 15 It consists of a probable on or centric fusion of two hromosomes of this group the whole hromosome count being 43 autosomes nd an XY sex chromosome complement. n 1960 Lejeune et al [7] described a case f a genotypic and phenotypic Kline- whose karyotype showed a centric sion of two chromosomes of the group 13-15 in addition to the sex chromosome berration a total of 46 chromosomes in ntrast to our case with 45 chromosomes nd a normal male sex chromosome

Two instances of a similar translocation recently been found in two clinically thy subjects, one in the U S (Cooper L. L. and Hirschhorn K personal comation) and one in Japan (Makino personal communication)

The other translocations so far desibed involved either a small and a large chromosome (Polani et l 4/*1 [11], Carter et al 15/*1 [3] Penrose et al 15/21 [10]; Turpin et al 13 22 [15]) two small acrocentrics (Fraccaro et l *1/22 [4]· Penrose et al. *1/22 [10]) or possibly a small acrocentric and a small meta centric (Böök et al. 19 *0/22 [ ])

Clinical Record

G J., born June 1955, had been placed in an institution for mentally retarded children, and from there he was referred to the hospital because of bilateral cryptorchidism and obesity His height being 99 cm at the age f 6½ years is 13 cm below the standard deviation, whereas his weight corresponds to his chronological age The bone age shows only a slight retardation but his dental age is grossly ret rded. His mental development is about 3 years behind the I.Q slowly regressing within the past 2 years as the child grows older Bilateral cryptorchidism was present the gonads not being palpable. The penis was small and the scrotum un developed. Clinically there were no other gross physical abnormalities except a convergent strabismus. Apart from an additional bilateral astigmatismus, the remainder of the ophthalmological examinat on was negative

The pneumoencephalogram showed a slight left hydrocephalus. The EEG was normal and the neurological examination was negat ve There were no pathological findings in the spinal fluid. Tests for phen ylketonuria, lues and t xoplasmosis were also negat ve

Growth hormone values were normal (32 microg)

TABLE 1. *Chromosome counts in cells from fascia lata.*

Chromosome count	Mitoses counted	Analysed by: Photography	Analysed by: Photography + karyotyping
1st biopsy: April 1961			
44	0		
45	54[a]	23	10
45?	2	1	
46	1[b]	1	
47	0		
Total	57	25	10
2nd biopsy: December 1961			
44	1	1	
45	47	16	7
45?	3		
46		1	
47	1		
T tal	53	18	7

[a] One tetraploid cell with 90
[b] Tetraploid cell with 92.

TABLE 2. *Chromosome counts in cells from the skin.*

Chromosome count	Mitoses counted	Analyzed by: Photography	Analyzed by: Photography + karyotyping
44	0		
45	12[a]	7	5
45?	4[b]		
46	0		
47	0		
Total	16	7	5

[a] Two tetraploid cells with 90.
[b] One tetraploid cell with 90?

Radioiodine uptake after 48 hours was 26 6 %, the PBI, however was within normal limits, i.e. 8.5 microg %.

The 17 ketosteroids and 17 hydroxy steroids were normal, 2.1 mg/24 hours each. *However neither the administration of* 11 beta-hydroxylase inhibitor (Metopiron) nor i.m. administration of ACTH caused an increase in the urinary output of 17-keto- and hydroxysteroids which might be interpreted as an insufficient response of the adrenals to ACTH.

Although the patient showed no signs of puberty and on histological examination of the testes there was complete absence of Leydig cells, urinary gonadotropins were found to be present, the values ranging between 15 and 23 units.

Serum electrophoresis showed a slight increase f the alpha and the gamma-globulin fractions. Aminoaciduria was 58.5 mg/day with an index of 1 6 %. Paper chromatography of the urine for aminoacids showed no bnormalities.

Serum electrolytes, BUN FBS P Ca and serum enzymes (SGOT SGPT LDH, SDH, alk. phosphatase) showed no deviations from average normal values except for a slight elevation of caeruloplasmin (71.3 mg %). Lipid metabolism showed some deviation from the norm. The P-lipids were normal but the optic density was well elevated above normal with a value of 0.77 The unesterified fatty acids were elevated up to 1000 mEq/l. Total lipids were also slightly above the average displaying a value 1 798 mg/100 ml. Cholesterol and cholesterol esters were normal.

Urine analysis revealed nothing unusual, i v pyelography concentration tests and excretion f phenol red gave normal results N renal clearance has been performed.

Unfortunately the family history which we were able to obtain is very poor partly due to lack f cooperation f the patient's parents, partly due t geographical factors. It seems to be non-contributory however Both f ther and mother were 25 years old at the time of the patient's conception.

Pathological findings

Laparotomy revealed two gonads measuring 15 8 7 mm each with the gross appearance f testes Epididymis and vas deferens were present. Biopsy *of the right testis* showed complete absence f Leydig cells. The tubules were small and narrow with

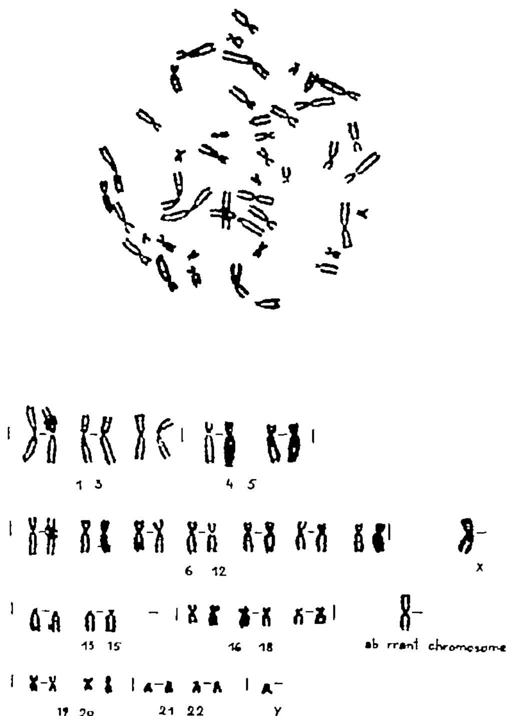


Fig. 1 Karyotype from fibroblast culture showing presumed translocation of wo hromosomes of group 13–15

TABLE 3 *Chromosome counts in mononuclear cells from peripheral blood.*

Chromosome count	Mitoses counted	Analysed by: Photography	Analysed by: Photography + karyotyping
43	2	1	
44	2		
45	13	4	3
451	9	4	
46	0		
47	0		
Total	[illegible]	[illegible]	[illegible]

only very few spermatogonia. They consisted of a single layer of epithelial cells and were separated by huge intertubular spaces. The basement membrane was normal, showing neither hypertrophy nor hyalinization.

Cytological examinations

The cytological observations were based on two primary fibroblast cultures with 12 subcultures, a skin biopsy culture with eight subcultures and a blood culture. The biopsies from fascia lata were taken on two separate occasions eight months apart one from the right thigh and one from the left. The skin biopsy and the blood culture were done t the time f the second biopsy f fascia lata.

he technique used for the tissue culture was that described by Lejeune Gautier & Turpin [8]. From the 14 slides of the first biopsy specimen we selected 57 undamaged mitoses, 5 f which were analysed in detail by photography and of those, 10 by microphotography plus karyo-typing. The results were consistent throughout. In that f the 57 metaphases examined 54 showed definitely 45 chromosomes and only four large acrocentrics of group 13–15. The same observation was made on 47 of the 53 mitoses from 12 slides of the second b opsy specimen, of which 18 were analysed by photography and seven by photography and karyo-typing. On careful observation we were able to identify the two missing acrocentric chromosomes as parts of an additional large or medium length metacentric chromosome. In most instances it looked very much like a chromosome number 3. Sometimes, however the two parts were almost separated and the two acrocentrics easily recognizable by size and shape.

The cultures of the skin biopsy specimen were not too satisfactory Of 16 mitoses examined we were able to confirm the modal number of 45 in 12 with certainty and in the remaining four with some probability We could never observe more than four large acrocentric hromosomes in any of them, and five karyotypes seem to prove the pre sence f the 13–15 translocation.

A blood culture done by the method of Hirschhorn (personal communication) was not successful enough to warrant any definite conclusions as to the presence of the above-described chromosomal aberration in the blood. Three karyotypes, however which we were able to construct from the best spread mitoses make it very likely Besides, the deviations were always below the modal number and in no instance did we get counts bove 45.

The counts are summarized in the accompanying tables.

Nuclear sex Examination of smears from buccal mucosa on two separat occasions showed a sex chromatin negat ve pattern.

Discussion

Several explanations of the origin of this chromosomal aberration are possible Most probably it originated during early embryogenesis of the patient by translocation of two large acrocentric chromosomes. It cannot be excluded, however that the translocation chromosome has been transmitted through several generations. Due to complete lack of cooperation on the part of the family we have not been able to examine the parents and siblings chromosome complement so far but we shall report on it as soon as information is

available. If the same aberration already existed in one parent, non-disjunction must have occurred during gametogenesis of this parent in order to produce a ∧ ×[1] gamete which after fertilization by a normal 6-acrocentric parent would result in our ∧ ∧ ∧ ∧ × zygote. Or else one parent with a purely hypothetical ∧ ∧ × × combination could have been fertilized by a normal gamete with three large acrocentric chromosomes, and this, too would give rise to a ∧ ∧ ∧ ∧ × zygote without non-disjunction during gametogenesis.

Still another possibility of origin would be the appearance of the translocation during parental gametogenesis only. There are several reports on inherited translocations in the literature [3, 10] most of them giving rise to no clinical abnormalities in the individual, unless an additional chromosomal aberration was present, such as trisomy. This has been explained by the presumably very small loss of chromosomal material occurring with a mere translocation of two acrocentric chromosomes. Turpin *et al* [15] however described a case with a probable translocation of chromosomes 13 and 22 without any additional numerical aberration. In this case there seemed to be a small but definite loss of chromosomal material. Clinically malformations of the spine were present (polydyspondylism) besides a moderate degree of physical and mental retardation. Our case could be another example of a severe congenital anomaly possibly caused by a mere translocation with very little loss of chromosomal material. There is no proof, of course, in either case that the chromosomal aberration is the cause for the clinical syndrome. On the contrary, the recent discovery of two instances of a similar translocation in clinically healthy individuals makes it seem more likely that the chromosomal aberration and the pathological conditions are merely coincidental.

The almost complete absence of spermatogonia in the biopsy specimen of the testis can be explained by the high grade cryptorchidism in this patient [13]. It does not represent any specific maldevelopment of the gonads.

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[1] Explanation of symbols: acrocentric chromosome of group 13–15. ×, two translocated acrocentric chromosomes of group 13–15.

Summary

The cytological observations of a 6-year old boy with mental and physical retardation, obesity and cryptorchidism are reported. Chromosome studies revealed a chromosome number of 45 and a consistent karyotype pattern with only four large acrocentric chromosomes of group 13–15 and an additional metacentric chromosome interpreted as the result of a translocation of the two missing chromosomes of group 13–15.

As far as our knowledge goes, this is the second case of a mere translocation of two autosomes associated with a severe developmental anomaly.

Acknowledgement

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CASE REPORT

Polymyositis in Childhood

A Case Report

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Few descriptions have been given of muscular affection in children in the form of myositis and then nearly always with the diagnosis of dermatomyositis.

Sands [10] described two cases, one with a chronic and one with a remittent course. Schrader [9] described three cases of his own and collected a further 19 cases of dermatomyositis in children under 7 years from the literature. Wedgwood *et al.* [12] described 26 cases. Of these 10 died, four still had the disease in an active form, four had contractures, and eight were almost normal. Roberts & Brunsting [7] described 40 cases; only two of them without disabling sequelae. Everett & Curtis [5] reported 19 cases of dermatomyositis, of whom 11 died and four continued to lead a more or less normal life. Charlisle & Good [2] described seven cases; one died and the rest, except for one, gradually became worse. Dachy [4] described a case in an 11 year-old girl with pronounced calcinosis.

Common to these reports is a rather uniform description of symptoms and course. Generally the onset of the disease is insidious, but it may be subacute. The principal symptoms are fatigue, low-grade fever, muscular weakness, skin involvement, most often edema, especially of the face. During the course of the disease a number of complications have been described. These include calcinosis occurring in about 15–30%, which is considerably more frequent than in adults; contractures, which are often the most frequent cause of disablement; cardiac symptoms in 10–15%, indicating impairment of the myocardium; and difficulty in swallowing and breathing. On the other hand, concomitant malignancy does not occur in children as often as in adults [6, 11]. Only a few pathological laboratory findings are described—i.e. slightly increased sedimentation rate, increased gammaglobuline and increased creatinine excretion. All authors stress that skin and muscle biopsy is crucial for the diagnosis, whereas electromyography is seldom mentioned.

The prognosis is always stated to be rather bad, as the disease may last from months to years and result in permanent disablement in more than half of the cases. A few have recovered almost without sequelae and a greater number with mild ones, and the rest have died.

However, it is remarkable that in all the cases reported, the diagnosis has been dermatomyositis in spite of the fact that not all skin biopsies were positive and not

all the patients had skin manifestations. Christensen & Levison [3] described six cases with the diagnosis of polymyositis two of whom were children. Walton & Adams [11] in a very comprehensive monograph, examined the literature and reported 40 cases of their own with the diagnosis of polymyositis. They point out that there is an acute and a subacute as well as a chronic form of myositis without skin involvement and that the prognosis is somewhat better than in the reports mentioned, as spontaneous remission may occur. The microscopic findings on muscle biopsy were the same as in dermatomyositis. We think it of interest to publish a case we have been following which illustrated the above.

Case Report

A seven year-old girl was admitted to the department in November 1961. She was normally developed and had previously been in good health. No diseases of childhood. Discharged in January 1962.

Present illness course and treatment

Four weeks prior to admission gradual onset of fatigue pain in the thighs and progressive muscular weakness were noted. On admission, she was unable to rise from the supine position without using her arms and found it increasingly difficult to walk. Her appetite was poor she felt chilly and had a diffuse headache. Immediately after admission, steroid treatment with prednisone 2.5 mg 2 and physiotherapy were instituted. Within 10–12 days the patient showed an improvement which continued throughout the following months. After 4 months, the patient still tires easily. The muscle test showed muscular power of 4–5, (4 = movement can be made against some outer resistance, 5 = normal). The treatment is well tolerated, her appetite has improved and she has returned to school.

Examination (only positive findings) Thin, pale.

Heart. Tachycardia (heart rate 100).

Neurological data. Head raised from pillow with reduced strength. Diffuse reduced muscular power of extremities, back muscles and abdominal wall. Muscular testing shows a muscular strength of about 3 (movement can be made with gravity as resistance). Difficulty in walking. Tendon reflexes slightly decreased.

Biopsy examination

(1) *Skin.* Normal epidermis and corium.

(2) *Muscle* (*vastus medialis*). The diameter of the muscle fibres is normal. In most areas normal transverse striation is present. However in scattered areas, muscle fibres are vacuolated and the transverse striation has dissolved. Interstitially there are many foci, varying from small to large, of infiltrates with lymphocytes, mast cells, plasma cells and polymorphonuclear and eosinophilic leucocytes. The sarcolemma nuclei are normally placed (signed Soeborg Ohlsen)

Electromyography

December 1961. Left biceps brachii denervation potentials of 2–3 msec duration, 30% polyphasic potentials. On voluntary effort a decrease in amplitude and duration of the motor unit action potential, while the number of action potentials relative to the strength of contraction shows an increase. On maximum effort mixed pattern to interference. Duration (40 potentials) 6.7 msec (normal 6.7 ± 20%). No effect produced by injection of synstigmine. Re-examination, March, 1962: same as December 1961 except on maximum effort interference. *Re-examination, October 1962.* Normal health, no complaints. Electromyography almost normal, only a few denervation potentials and a slightly increased polyphasic potentials. Muscle biopsy (vastus medialis) myositis interstitialis nodularis chronica with secondary muscular dystrophy (as suggested above).

Comment

The patient unquestionably has myositis. This was verified by muscle biopsy and electromyography which apart from the expected decreased mean potential duration, also showed denervation potentials This may however be seen in severe cases of myogen affection [1].

In spite of the severe myopathy the creatinine excretion was normal, which seems peculiar Tachycardia associated with an increased transaminase level may indicate myocardial involvement. In our case the diagnosis of polymyositis must be preferred to dermatomyositis because of the absence of skin involvement, both clinically as well as on biopsy Walton & Adams [11] indicated that polymyositis often has a milder course than dermatomyositis. In our case the patient also recovered with surprising rapidity but this was hardly due to a remission as improvement immediately followed the institution of steroid therapy

In several of the reports mentioned, steroids have been used and all stress either lack of effect or short symptomatic remission. In this case, however after a few months of steroid treatment significant improvement occurred, as the patient now runs normally and almost all the muscles have been tested to 4–5 However repeat electromyography still showed denervation potentials in spite of pronounced clinical improvement in muscular strength, and this confirms that steroids have no curative effect On the other hand the decreased transaminase level may be due to the steroids, and this would support the concept that they retard the progress of the disease.

In our case the etiology is also unknown. Although myositis in children is rare and partly differs from that occurring in adults, the pathological picture is characteristic. Furthermore it seems reasonable according to available data to distinguish between two groups—i.e. dermatomyositis with a rather bad prognosis little affected by steroids and polymyositis with an undoubtedly better prognosis more affected by steroids. This treatment perhaps retards the progress of the disease and results in a quiescent state that on subsequent microscopy may resemble muscular dystrophy [8].

Summary

A case of polymyositis in a 7 year-old girl, verified by electromyography and biopsy is described. The difference between dermatomyositis and polymyositis is discussed. According to the literature polymyositis appears to have a better prognosis. In th case reported, steroids were beneficial. This treatment is discussed

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CASE REPORT

Intraspinal Dermoid Cysts in Children

Survey of Literature and Own Cases

by GUSTAF PETTERSSON and KERSTIN WERKMÄSTER

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The group of congenital malformations to which intraspinal dermoids belong is to be found in the literature under a variety of names. No consistent nomenclature xists, but titles in current use are: der moid cysts, epidermoid cysts, congenital lermal sinus, teratoids, teratomata or holesteatomata.

Approximately 150–200 cases of intra pinal dermoid cysts have been reported. f these, 80 % have been seen in paediatric ractice mostly in the age group 0–5 years. ymptoms seldom have their onset in the lder age groups. The sex distribution is bout equal.

As early as 1755, Verratus described the rst case of dermoid in C.N.S. Boström, in 897 pointed out the epithelial origin of hese structures. In all English-speaking iterature Moise is quoted as the first to lescribe case f congenital dermoid cyst within the C.N.S. communicating with the kin. H described, in 1926, case f taphylococcal meningitis secondary t acral intraspinal dermoid cyst with skin stula.

In 1941 Sjövall described a subdural ermoid cyst associated with spina bifida, n which a fistula had formed t the skin. The levelopment f neuro-surgery first led t areness f the importance f early diagnosis and early operative treatment in such cases.

Congenital dermoid cysts result from ectodermal dysplasia, during the development of the neural t be The development f the neural tube normally takes place during the first foetal month, and according to Matson & Ingraham [5] this abnormality arises when the neuro-epiderm separates from the epithelial ectoderm, during the 3rd–5th weeks of foetal life. The epithelial defects thus arising may extend t varying depths. They may end immediately beneath the skin, or else extend into the C.N.S., and communicat directly with the central canal or the ventricular system. Dermoid cysts are often accompanied by other signs of abnormal development, such as spina bifida occulta.

The intra-spinal dermoid usually consist f a sausage-shaped cyst Its extent may vary and may include several vertebral segments. The majority f these dermoids are situated subdurally but extradural and intramedullary forms have been described. The lumbar region is the site f predilection, the incidence decreasing higher up the spinal column. Henschen [4] maintains that spina bifida occulta can be diagnosed clinic ally as well as radiologically in 20 % f cases.

Dermoid cysts in the C.N.S. grow very slowly More than /3 f these patients have sought advice for infection and a localized abscess in the spinal canal has been discov

ered in most cases. Those which have no communication with the skin, have long latent periods without symptoms. Functional disturbances appear lat if at all. In contradistinction, the great majority of dermoid cysts with skin fistulas become infected early in life

Treatment is operative and consists of the complete eradication of cyst and sinus. Where the cyst is extradural, it can sometimes be excised *in toto* without opening the dura. If the fistula continues through the dura, then this must be opened in order t excise the cyst as completely as possible Should the cyst lie within the spinal cord, one must be content with emptying it and carefully scraping out the cyst wall, so as not to cause neurological damage.

The prognosis for intraspinal dermoid cysts, even when complicated by meningitis, is relatively favourable.

During 1955 two cases of intraspinal dermoid cyst with skin fistula were admitted to the Children's Hospital, Gothenburg Both were operated on successfully

Case I

Boy aged 2 years and 3 months. Admitted to hospital 17 I 1955 No family history of congenital deformities. Pregnancy normal. Uncomplicated parturition 24.2.1952. Birth wt 2000 g. Healthy and developed normally until May 1954. At the age of 1 year and 8 months, the child developed fever and stiffness in both hips. The pyrexia persisted for 14 days and as no improvement occurred he was admitted to the local hospital for investigation on 19.5 1954. No definit physical abnormality was noted. Terramycin was instituted with some improvement, although low-grade fever persisted. One week later the temperature rose again. L.P was carried out and the C.S.F was found t have an elevated protein and 1272 cells. Bacterial culture was negative. Streptomycin was substituted for terramycin, and gradual improvement followed After 2 months, the patient became asymptomatic and was discharged. Two weeks later fever recurred, accompanied by diarrhoea. On August 17 1954 he was re-admitted with severe meningitis, and was found to have a markedly raised cell count in the C.S.F and growth of coliform bacteria on culture. Following treatment with various antibiotics, he again became symptom-free. On re-examination a small red spot, about 1.5 cm in diameter with a tuft f hair in the middle, was detected in the sacral region. A tiny opening was present in the centre, from which a trace of pus had run each day since the beginning f Nov 1954 X-ray of the lumbar region revealed a defect in the dorsal arch of L IV On surgical consultation, a fistulous tract to the spinal canal was found. On suspicion of an intraspinal dermoid cyst which had become infected, resulting in recurrent meningitis, the child was immediately transferred to the Children's Hospital in Gothenburg.

On examination a light red naevus over one cm in diameter with a tuft of hair in the centre was present in the mid-line at the level I S 1 In the middle of the hair tuft was the fine orifice of the fistula. On palpation there appeared to be some thickening of the subcutaneous tissue with adherence to the deeper structures. The sphincter ani appeared to have decreased tone, but no other abnormal neurological signs could be eli ited.

On Jan. 27 1955 the fistula was incised. Two days later symptoms of meningitis recurred with high fever and nuchal rigidity After 2 weeks, he became afebrile and was again operated on. The skin lesion and fistular tract about 3 mm in diameter were excised. When it became apparent that the fistula entered the spinal canal, it was ligated and divided at the level. Histopathological examination revealed meningocele communicating with a dermoid cyst Fistula formation recurred and a more radical peration was performed on March 19 1955. Following the fistula inwards, a spina bifida occulta involving two vertebral arches was discovered. The defect was *filled*

a fatty mass through which the fistula 1 Laminectomy was performed and subdural, sausage-shaped dermoid cyst found, involving two vertebral bodies. ne cyst, being adherent t the nerve roots, ould not be totally extirpated. Its contents scraped out and the inner cyst wall ft in situ. Post-operatively the patient ed 400 000 I.U penicillin daily Pro- was satisfactory and the patient was scharged weeks after the operation, in ood health. At follow-up 5 years later the atient s condition was very satisfactory

ase 2

Infant girl aged 14 days. Admitted to the hildren Hospital July 21 1955.

Pregnancy and parturition normal; birth 3780 g. It was noted at the maternity linic that in the dorsal mid-line, level with IV the child had a round red spot bout cm in diameter with a purulent ulceration the centre. N neurological disturbances ould be detected. She was transferred to us ith the diagnosis f spina bifida with lceration X-ray of the lumbar region howed dorsal to the vertebral spine f IV ossification of an area about 1 cm ½ cm. There seemed to be a corresponding displacement of soft tissues. These changes were thought to indicate the presence of a dermoid. Operation was carried out on August 2, 1955. A fistula was discovered, tracking in t the lig interspinosum and in between the spinal processes. There was an bvious widening f the spinal canal t the level of entry of the fistula. Laminectomy was performed and a dermoid cyst the size of a finger tip was ituated extra-durally and could be totally extirpated without entering the dura. The cystic contents appeared to be calcified; the histo-patholog ical report was an inflamed dermoid cyst Preoperatively the patient was given peni cillin for 8 days, and following operation, a combination of streptomycin and penicillin. The course was uneventful, and the patient was discharged 10 days after operation. She was seen at follow up 5 years later and had been symptom free.

Summary

Report of two cases of successfully operated intraspinal dermoid cysts

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SUMMARY OF SUPPLEMENTS

The Proceedings of the Thirteenth Northern Paediatric Congress

Copenhagen June 25–June 28 1961

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(*Supplement 140*)

Late Prognosis in Tuberculous Meningitis

A Clinical Neurological Ophtalmological, Otological Psychological, Psychiatric, Electroencephalographical, Radiological and Sociomedical Study

by OLE WASZ-HÖCKERT and MARTA DONNER *with the collaboration of* PENTTI MIETTINEN JAAKKO RANTA, RIITA PENTTI EERO VALANNE, JYRKI KAUTHIO and PER ERIK HEIKEL

(*Supplement 141*)

Contents.

Adenovirus Infection in Childhood

An Epidemiological and Clinical Survey among Swedish Children

by GÖRAN STERNER

(*S pplement 14*)

A series of investigations of adenovirus infections in Swedish children has been carried out since 1954. The results are reviewed in this paper and are discussed in relation to experiences of other authors, with particular emphasis on the evaluation of the role of adenoviruses in the development of various clinical signs and symptoms.

Adenovirus types 1 2, 3 4 5 6 and 7 have been encountered from children liv ing in Stockholm or Malmö Serological studies on healthy Stockholm children showed that type infections dominate in the age group of 1–3 years as well as that of 10–1 years. Among the small children 7 % had neutralizing antibodies to type 2, among the older children not less than 71 %. Antibodies to one or more of types 1 2, 5 and 7 were found in 3 and 85 % respectively

During a period of one year stools were collected from children at the time of admission to the Children's Hospital in Malmö for a virological study The in cidence of adenoviruses was 5 9 % in cases with signs and symptoms of cute respira tory illness and only 0 0 in children with various non-contagious diseases. highly significant difference The isolated adenoviruses belonged mainly to types 1 and 5; only a few proved to be types 4 6 and 7 Adenovirus types 1 nd 5 were found in children from 3 months to 3 years old, half of whom were below one year of age The frequency of excreters of adenovirus types 1 2 and 5 among children hospita lized with acute respiratory illness in Stockholm was found to be similar to that in Malmö Most of the Stockholm children with types 1 or 5 adenovirus were also below 3 years of age

Adenovirus type infections were on the other hand, chiefly found in school children, but were also observed in infants and small children. The incidence of types 3 and 7 infections has been found to be fairly low among Swedish children during periods with no epidemic outbreak of such infections. Thus th study in Malmö co vering also the autumn of 1959 showed only a minimal frequency of type 7 infec tions and type 3 was not isolated t all. On the other hand, the frequency of type 7 infections among tested children with acute respiratory illness admitted to two hospitals in Stockholm during this parti cular period was sometimes (Aug –Sept) 50 or higher Epidemiological nd serological evidence showed, however that this outbreak of type 7 infections in Stockholm in 1959 was not an xtensive one

Adenoviru infections can be symptomless or cause only mild illness. Th frequency f such symptomless infections could not be estimated in our studies.

Our results show a correlation between the recovery of adenovirus types 1, 2, 5 and acute respiratory illness in children. During an epidemic outbreak type 7 was correlated with a syndrome of fever pharyngitis, conjunctivitis and gastroenteritis. In other Swedish outbreaks adenovirus type 3 was associated with a similar syndrome.

Adenoviruses have been encountered in only a few cases of atypical pneumonia in Swedish children.

The prognosis of adenovirus infection is in general good. Fatal cases in infants and small children with atypical pneumonia have been observed, however, in association with adenovirus infection in various countries but not in Sweden.

Paroxysmal Tachycardia in Infancy

A Clinical and Experimental Study

by ÅKE LUNDBERG

(*Supplement 143*)

The literature on paroxysmal tachycardia in infancy shows a lack of numerically large series whose case records have been analyzed by a single author or team of authors. No detailed, systematic follow up studies have been published. Moreover the diagnostic criteria seem to be insufficiently authenticated. Although parental factors have been surmised to play an aetiologic role, they have not been thoroughly investigated. Post-tachycardiac ECG changes have long been known to exist, but their relation to the ventricular rate during an attack has not been pointed out, nor have any experimental studies been made in animals. Finally our knowledge of the relation between paroxysmal tachycardia and pre-excitation is far from complete.

The main object of the present investigation was to elucidate these problems, by analyses of a series of infants with paroxysmal tachycardia collected from all the paediatric departments in Sweden.

Clinical study

A brief survey is given of the historical aspects of paroxysmal tachycardia, with emphasis on its occurrence in infancy.

The way in which the present series was collected and analyzed is presented. ECG recording by means of an oesophageal lead is described and commented on.

An ECG recording during an attack is a prerequisite in every case. For a definite diagnosis of paroxysmal tachycardia (PT), these tracings must fulfil one of the following criteria.

1 Atrial or ventricular rate ≥250/min.

.. With an atrial or ventricular rate <..50/min, one of the following sub-criteria

A. Alternating sinus rhythm and ectopic tachycardia

B Isolated extrasystoles after the attack, with QRS complexes of the same configuration as during it.

3 A heart rate <250/min (but >200/min) combined with observations during hospitalization of definite alternations in heart rhythm.

Paroxysmal tachycardia is accepted as supraventricular when a mutual relation is present between atrial and ventricular complexes. The P wave can be distinguished from the T wave *in only a few cases*; in the others a QRS complex of normal duration for the age is taken as a criterion of the supraventricular origin of the impulses (PST).

The P wave cannot be identified in any of the cases with an berrant QRS complex, so that a dissociation between atrial and ventricular rhythm cannot be demon strated. Consequently the series contains no definite case of ventricular tachycardia. The cases with an aberrant duration of QRS are therefore denoted as paroxysmal tachycardia with impulses of unidentifiable origin (PT_u).

PST in the limited sense flutter and fibrillation are defined on the basis of the presence or absence on the ECG of the waves typical of these disorders.

The series comprises 54 infants; PST_L is present in 39 cases flutter in 9 and PT in 6

Totally 63.5 are boys.

At the onset of PT 7.... per cent of the infants are less than 2 months of age in 6 *of the 54 cases intrauterine PT is suspected.*

The geographical incidence seems to be even.

An attempt is made to account for various factors that can be envisaged as being of aetiologic importance in paroxysmal tachycardia in infants The analysis is based on data in the medical history of the parents and their current mental stat as well as data in the obstetrical records of the mothers, and in the case records of the infants.

Investigation of the parents discloses a notably high incidence of *repeated attacks of syncope in the mothers and of peptic ulcer in the fathers* In addition, the current examination shows *a somewhat high in cidence of neurosis in both mothers and fathers*

The series contains a significantly *higher incidence of older primiparas* than that in the general population of Sweden.

The case records of the infants reveal two cases of severe cardiac malformations, and one case of myocarditis, all verified at autopsy

In the present series, symptoms and signs that may be common to infection and heart failure are presumably to be ascribed more often to the latter

After discussing the diagnostic difficulties that may arise without access to ECG records, an account is given of the clinical features in the present series The *current symptoms* are dominated by unwillingness to eat, an unnatural skin colour an abnormally raped heart ction and respira tion a well vomiting

In addition to tachycardia the salient features *at examination* are liver enlarge

ment (35 %) cyanosis (68 %) and subnormal temperature (31 %)

The signs of congestive *heart failure* in this age group are discussed, and it is concluded that liver enlargement and/or cyanosis are the most reliable criteria. Based on these criteria heart failure is present in 2/3 of the infants in the present series without evidence of A—V block (PST and PT_a) and in half of those with manifestations of A—V block (flutter)

The grade of heart failure seems to be dependent on the ventricular rate during a paroxysm. Since the duration of tachycardia cannot be determined with satisfactory accuracy no comments can be made on the influence of this factor on the grade of heart failure in the present series

The ECG recorded during the first verified attack of PT more often shows a lower ventricular rate in infants less than 14 days old than in those above this age This has earlier been found to apply in infants with normal heart rhythm as well.

On the ECG after a paroxysm the amplitude of the P wave in lead II is abnormally high in 80 9 % of the cases. The rise in amplitude seems to be correlated to the ventricular rate during the paroxysm.

The amplitude of the T wave measured in lead I, *is normal in most cases*. This discrepancy between the incidence of a P wave and a T wave of abnormal amplitude is attributed to the large preponderance *of cases of supraventricular PT*

Pre-excitation is present on the post-tachycardiac ECG of 51 % of the children. This incidence is considerably higher than that reported earlier The reason is probably to be sought in the number of recordings made, as well as in the period covered by them.

The children with pre-excitation are found to have a higher mean ventricular rate during the primary attack of PT than those who do not exhibit this phenomenon. The difference is highly significant.

This finding raises the question of whether pre-excitation may not, in fact, be a sequela of paroxysmal tachycardia. This supposition is in contrast to previous discussions of the causal relation between paroxysmal tachycardia and pre-excitation when the reverse has generally been considered to apply

A follow up study is made of 47 of the 49 surviving children. The median duration of the observation period is 3 years 11 months.

The mortality is 9 % in the whole series; it includes no case of flutter

A recurrence of PT verified by ECG is found to have taken place within one year of the primary attack in 35 % of the cases. If unverified recurrences are included, the figure rises to 65 %. Recurrences are infrequent more than one year after the onset (verified 7 % total 12 %)

In 57 % of the cases with pre-excitation during the first year after the onset of paroxysmal tachycardia it was still present of ECGs recorded after this time. *It is pointed out that when pre-excitation* does cease, this seems to occur during the first year after the onset of PT otherwise, it has a tendency to persist.

Psychiatric examination shows a somewhat high incidence of neurosis (*16 %*), probably attributable to the parents over protective attitude. The I Q. follows the normal distribution.

The height and weight are within the normal range in 91.3 % of the children.

The incidence of congenital organic heart

disease is not higher than could be expected at the onset of paroxysmal tachycardia.

Earlier post-tachycardiac changes in amplitude of the P and T waves are no longer present except in one case with a short observation period.

Ectopic rhythm in the form of extra systoles is present in totally 11 % of the cases (on the resting ECG in 6 %) an incidence that does not seem to differ from that to be anticipated in healthy children.

An exercise test can be performed in 13 children. It gives no evidence of a higher incidence of ECG changes as in orthostatic reactions than in the normal population, nor of a decreased physical working capacity

Pre-excitation is present on th ECG in 14 children, in 10 it is of group A and in 4 of group B, classified according to Rosenbaum *et al.* Spontaneous variations are observed, but in no case does pre-excitation disappear completely

In 4 of 44 children (9 %) the EEG shows activity that cannot be regarded as normal for the age an incidence that presumably does not differ from that in a normal population. This argues against any relation between paroxysmal tachycardia and persisting EEG signs of cerebral dysfunction.

Experimental study

The method devised by the author for inducing atrial tachycardia of high frequency without the necessity of thoracotomy is described and discussed.

Young pigs are used as experimental animals Atrial stimulation is induced by a pace-maker (PMr) designed for clinical purposes, modified to generate impulses of considerably higher frequency The intracardiac PMr electrode is introduced percutaneously into a neck vein and advanced into the right atrium. The position of the catheter tip is determined by studying the configuration of the atrial complex in lead VRA. In 85 % of the 39 animals the assumption of cardiac rhythm by the pace maker is found to be optimal with the electrode tip in the superior part of the atrium.

Atrial tachycardia, with retained 1 1 A—V conduction, and a duration of 24 hours, is induced in 17 young pigs

During induced tachycardia an increase in the mean amplitude of the T wave is observed in the right chest lead Immediately *after* the cessation of tachycardia, an increase in amplitude occurs in the animals with the highest ventricular rate during the experiment whereas a decrease in amplitude of the T wave occurs in those with a lower rate (Fig 22)

The changes in amplitude of the T wave observed in these expriments are in agreement with those seen in human subjects during and after physical work

Diabetic Schoolchildren

by GÖRAN STERKY

(*Supplement 144*)

The purpose of the present work was to study the social somatic and mental states among diabetic schoolchildren, especially in the puberal ages, and to collect information of biochemical and clinical nature on the children before vascular lesions have appeared in an attempt to establish criteria for the determination of susceptibility to diabetic angiopathy

The *material* consisted of 147 diabetic children 68 boys and 79 girls, out of the 165 children with diabetes in the schools of Stockholm A matched control material of 131 non-diabetics (61 ♂ 70 ♀) took part in the various investigations. The mean age at onset of diabetes was 7 years and the mean as well as the median duration around 5½ years. Fifteen per cent were clinically diagnosed as having moderate retinopathy and/or nephropathy

The *prevalence of diabetes* in the age 7–14 years was calculated to 1 44 mille.

The *socio-economic background* among the diabetics did not deviate from that of the general population.

School achievements were equally well performed by diabetics and non-diabetics.

Mentally disturbed children were found as often among diabetics as among non diabetics, but the diabetics had somewhat more serious and more frequent symptoms per case, especially noticeable in the post-puberal ages. Diabetic *mothers* were mentally disturbed (usually anxiety symptoms) more often than "non-diabetic mothers

The *height* of diabetic boys was less than that of comparable controls. Teenage diabetic girls *weighed* somewhat more than the non-diabetic girls. Diabetics and non-diabetics did not differ as to *blood pressure*.

Diabetic children before the age of 15 had a somewhat increased frequency of *acute infectious disease* but the diabetics capacity for *antibody formation* seemed to be intact.

The three main aspects of diabetic treatment—insulin diet and exercise—were studied in detail.

Girls received higher *insulin* doses than boys and also showed more skin reactions to insulin.

Caloric consumption was lower among diabetics than among non-diabetics. Both series tended to have a low intake of vitamins and minerals especially of iron. Certain of the intentions behind dietary prescription seemed to have been fulfilled among diabetic boys

Diabetic children, after the early teens, tended to have a lower *physical work capacity* irrespective of type of calculation, than corresponding non-diabetics. Participation in physical training declined by increasing age among diabetics.

The *diabetic control* was judged mainly on the basis of the degree of glycosuria. The patients were referred to three classes of diabetic control, excellent "fair and

poor" Roughly half the material was designated as being of fair control. The degree of diabetic control showed no connection with the capacity for antibody formation or physical work capacity

On the basis of the i tensity of treatment the diabetic series could be divided into two almost equally large groups. Caloric consumption was lower among the intensely treated group. No case of clear diabetic incompensation was found among them nor did they show any increased frequency of mental disturbance. Only 10 % of all cases of poor" control were found in this group

The various *biochemical components* studied in the blood revealed elevated mean values for the diabetics in most fractions significant for α_2-globulins cholesterol and phospholipids and for hexoses and total protein-bound carbohydrates in certain age groups. Age and sex as well as angiopathy and degree of control were almost without influence.

Knowledge of the values for glucoproteins, glycerides and free fatty acids in *normal* children is scanty and therefore the results obtained in the control material are of certain worth in themselves.

Family history of cardiovascular disease was met with as often among diabetics as among non-diabetics and the frequency seemed to tally with that in any population. Diabetic heredity equally frequent in all age-at-onset groups was suggested as being different from cardiovascular disease heredity

The observations made formed the background to a discussion around proneness to angiopathy Without knowledge of a deciding risk factor all findings seemed to be of value The standardization f conditions in the study afforded certain basic data for the preselection of juvenile diabetics with proneness to angiopathy A follow up will show their worth

Evolution of the Electrocardiogram of Healthy Premature Infants during the First Year of Life

by S. ZOE WALSH

(*S pplement 145*)

Serial electrocardiograms of 8 healthy premature infants during their first year of life were studied. Weight differences were found to be largely inconsequential. The tracings re similar to those of full term infants, except during the first week of life High mplitude deflections are characterist c of infancy With ge intervals become longer and size of deflection increases. Tables on these measurements are included. Characteristics which may prove useful in the recognition of ventricular hypertrophy are mentioned. Possible explanations of the findings are discussed.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Finnish Pediatric Society

Meeting, April 7 1962

James A Miller J., New Orleans: Some Unconventional Approaches to the Problem of Asphyxia of the Newborn.

Although deaths during the first year of life have fallen strikingly in the U.S.A. since 1915, the decrease in deaths of viable infants during the first 24 hours has not kept pace and instead of comprising only one seventh of the total they now make up one third of all the deaths during the first year. Since autopsies incriminate asphyxia as the largest single cause for such deaths the possibility suggests itself that conventional methods of resuscitation are inadequate and completely new approaches to the problem are needed.

One of the simplest and the most effective method for protecting against death from asphyxia in our experiments has been hypothermia. It has been found to increase *asphyxial survival in neonatal guinea pigs*, piglets, kittens, rabbits, and puppies (listed in order of increasing effectiveness). Of these, puppies are born at a stage of development most similar to that of the human neonate. In puppies 15°C body temperature gives maximal protection against asphyxia. At this temperature survival time averaged 7½ times that of normothermic controls and all animals removed from the asphyxial chamber after 4 times the lethal exposure recovered spontaneously. Spontaneous recoveries of 15°C animals have occurred from as long as 10 times that which was lethal for normothermic littermate controls. Cooling need not precede asphyxiation. Puppies and kittens cooled after 7 minutes of asphyxiation while normothermic (½ lethal exposure) recovered spontaneously from exposures which were lethal for normothermic controls. In addition, mild asphyxia during or just before cooling increased resistance to total asphyxiation by about 50%. Therefore mild asphyxiation can be considered as "premedication" for the induction of hypothermia. *Sedation prolonged asphyxial survival* and its effects were enhanced by hypothermia. Intragastric oxygen was without benefit in normothermic animals, but produced a significant prolongation of life in hypothermic animals.

Transfusions of oxygenated blood have been tested in previable prematures. When blood pressure was near zero intravenous transfusions were of no benefit. However the same volume introduced intra-arterially induced effective pumping action on many occasions, and often restored normal blood pressure. Contrast radiography showed that *under conditions of zero blood pressure* intravenous transfusions pool in the liver, portal system and venae cavae. By contrast, intra-arterial transfusions fill the coronaries after 4–6 ml and the basilar artery by 10 ml. Asystolic hearts of prematures have been successfully started by intra arterial transfusions of oxygenated blood, and Westin reports that transfusions of cold, oxygenated blood are effective in asphyxiated infants being treated by hypothermia.

It is important to determine the rates at which organs of different sized fetuses can be cooled. Thermistors in heart brain, colon, esophagus, and skin of unembalmed stillborn fetuses (weight between 451 g and 4107 g) showed appreciable cooling in 15-20 min even in the largest fetus. Depilated

adult guinea pigs (451 g–1186 g) with similarly placed thermistors were cooled once while alive and a second time after death to determine whether cooling occurs more rapidly in living or dead organisms. In all organs tested with the exception of the skin the temperatures f ll more rapidly during the first cooling period (when the heart was pumping effectively) than during the second (after the animal had died). Thus, it is anticipated that the cooling rates of living human infants will be appreciably greater than those of stillborns.

It may be concluded that in experimental animals hypothermia not only *postpones* but also *prevents* death from asphyxia. It is especially effective in sedated animals, and the combination of hypothermia with transfusions of oxygenated blood can restart hearts in asyst le. In addition, if not too severe, asphyxia before or during cooling enhances the ability of hypothermia to protect against a subsequent exposure to total asphyxiation.

B. Westin, Stockholm: Hypothermia in the Treatment of Neonatal Asphyxia.

In spit of the fact that the influence of temperature on metabolic requirement is well known, until 1959 no real attempt had been made t determine whether the response of asphyxiated newborn infants to reduction of body temperature is similar t that of other newborn mammals. In guinea pigs, rabbits, kittens, and puppies, Miller & Miller found that hypothermia not only postponed, but prevented death from asphyxia. In addition, animals in which cooling was initiated after the induction of asphyxia recovered completely and spontaneously from an exposure which was lethal for warm littermate controls.

I 1959 a preliminary report was published on the first six cases in which cooling was used for treating asphyxia pallida and recently the first 10 cases were reported detail. One of these with an pnoeic period of 79 min, recovered from the initial asphyxia, but subsequently succumbed at 30 hours from respiratory distress. The remaining nine infants ha been given ECG EEG hearing and development tests and have been subjected t multidisciplinary evalua tion by a team of pediatricians. According t all criteria, the infants, including one which was pneic for 5 minutes, are in good health and developing normally

Since January 1960 hypothermia has been employed in all cases of neonatal asphyxia t the Sabbatsberg Women Clinic, Stock holm, in which conventional resuscitative measures have been ineffect ve or asphyxial depression has been profound The present series consists of 65 cases (1 of 4465 infants). The maximum Apgar score was 3 and most infants had a score of only 1 Generally before cooling was initiated, artificial respiration or gastrointestinal in sufflation had been tried without benefit In 57 infants hypothermia was supported by oxygen administration. In the remaining eight cases, hypothermia was supported by transfusions of oxygenated blood. In all 65 infants the immediate result of the treatment was good. However 13 (20) died within 48 hours. The remaining 5 infants (80 %) are alive nd well t the time of writing Only four of the infants who died were mature Three of these were found t be intra-cranial hemorrhage at autopsy and the fourth had congenital heart defect which probably contributed to the death of the infant.

Among the nine prematures who died, two had intracranial hemorrhages nd two were extremely small (550 and 750 g). For the remaining five which weighed between 1770 and 1900 g no causes of death other than prematurity and asphyxia were found. In our hospital live-born infants in these weight ranges have a mortality of 3 t 25 %. Of the 52 surviving infants, 4 had an uneventful neonatal period. F ve had tran sient signs of CNS disturbance which did not extend beyond the neonatal period. One which was subjected t second period of cooling, had a transient subcutaneous dystrophy of the left arm. All 52 infant have been found to be w thin normal ranges of

of nine years, in other age groups the correlation is very slight.

R. L. Takkunen and *M. Frisk*. Small Prematures at 6– Years of Age

A report is given of a study on the development of small prematures. The results of recording the physical and intellectual status of 4 children, aged 6–7 years, who were born prematurely with a birthweight of less than 1 00 g are presented. They were found to be in the average of smaller stature than full term children of the same age though great variations were recorded in the individual measurements. Their general condition of health was good. Subnormal vision and adenoid vegetations were present in unusually many. The most significant finding was the great amount of signs of neurological lesions, especially in the motorical functions, though also in the intellectual and other psychological functions. An attempt is made to correlate these findings with the symptoms and signs of the early development of these children. Single borns and twins are treated separately in the material and significant differences between them are established the children of the twins-group being obviously much more mature in spite of their birthweight and thus less liable to injury

K. Kos almaen, L. Hjelt and *N. Hallman* Immunological Studies in Congenital Nephrosis.

(Published in *Amer J Dis Child, 101* 544 196 and *Ann Paediat Fenn 8* 173 and 181 196.)

T Peltonen and *L. H rvanen* The Ductus Venosus.

The ductus venosus is a continuation of the umbilical vein and drains into the left hepatic vein. It is funnel-shaped, expanding in the direction of the blood flow At the point of outset there is an annular sphincter muscle The sphincter regulates the flow of blood entering the inferior vena cava and protects the fetal circulation during uterine contractions against too rapid changes in volume The umbilical vein is also capable of local contractions and contracts rapidly into a narrow thread after clamping of the umbilical cord. The ductus venosus remains patent temporarily after birth and volume changes are encountered in it. It can be visualised in man (15 newborns) by means of radio-opaque material for at least 12 days, but the flow can even halt completely at times. Noradrenaline adrenaline (dose 25–1000 γ) and acetylcholine (5–1000 γ) open or dilate the ductus venosus. Histamine (200–1000 γ) has no effect. A test series was performed on newborn lambs, cats and dogs (*03 umbilical angiographies) and the reactions were found to be similar in anencephalic and mongoloid children. In lambs the ductus venosus is generally patent on the 1st 3rd day; it is closed, but opens when the above vasoactive agents are administered on the 4th–6th day After that these agents have no influence. The final answer has still to be found to the question whether the ductus venosus has a postnatal function. There are animals such as the pig and the horse in which the ductus venosus is closed and disappears prior to birth, but it seems obvious from contrast medium studies that the pig nevertheless has variable short circuit communication from the portal circulation to the hepatic veins.

M Dahl Intracardiac Ph nocardiography

A report is given on the methods used in intracardiac phonocardiography on the basis of the literature and of 50 own patients with diagnosed or suspected congenital heart disease A phonocatheter made by American Electronic Laboratories Inc was used in the study It was verified that both normal sounds and murmurs are loudest at the site of origin and move from there primarily in the direction of the blood flow A murmur

that originates in the ventricle for instance is not heard in the atrium and murmur originating in the pulmonary artery is not audible in the ventricle

I the right atrium the first sound was louder than the second sound in the cases studied. In patients with an atrial septal defect there was no systolic murmur in the atrium but sometimes a faint diastolic murmur

I the right ventricl the heart sounds were noticeably louder *than in the atrium. The* first sound was louder than the second sound. I cases of ventricular septal defect with a left-to-right shunt the intracardiac phonocardiogram showed a systolic murmur but with right-to-left shunt no murmur was found *in the* right ventricle In patients with an atrial septal defect a faint systolic and diastolic murmur could be heard in the right ventricle.

I the pulmonary artery the finding varied considerably in different parts and different cases. Valvular pulmonic stenosis caused diamond-shaped systolic murmur shortly after the first sound with diminished second sound. In cases of infundibular pulmonic stenosis the murmur began with the first sound.

I patent ductus arteriosus the characteristic machinery murmur was audible t the loudest in the pulmonary artery t the opening of the ductus. In the periphery it diminished and the diamond-shaped form became more even in amplitude The machinery murmur was not audible in the aorta.

The increased blood flow in atrial septal defects caused here systolic murmur which was the same as the systolic murmur on the chest

With the phonocatheter it has been possible t localize precisely cases of septal defect and patent ductus arteriosus in which oxygen analyses did not give positive diagnosis. Because of softness of the phonocatheter used by us it has not been possible in certain cases t enter all necessary places, e. the pulmonary artery

The phonocatheter has proved to be valuable instrume t in certain defects, in which the diagnosi is difficult or in which a precise localizatio of the defect is important

H Åkerblom and *O Somersal* Absorption Capacity f the Rectum.

The absorption of glucose from the rectum was studied by means of generally labelled C^1 *-glucose 5.6–10.0 microcuries were given* in a 5% glucose sol tion into the rectum of 13 hildren aged 3 years and 11 months to 14 years and 8 months, suffering from acut leukemia or some other malignant disease Fifteen experimental series were performed. *In* eleven cases C^1 -glucose and normal glucose (carrier) were gi en in a small volume (7–65 ml) whereas in 4 cases the volume of the glucose solution was 230–300 ml. The glucose solution wa pplied in all cases at a rat of 1 ml min. After application of C^1 -glucose expired air was collected for 6 t 10 hours, urine for bout 24 hours and stools for from 4 hours t 5 days. The results were obtained by measuring the radioactivity in expired air urine and stools and comparing them with the given dose When using a small volume there was a distinct and rapid rise in the specific activity of the expired air during the first few hours after pplication. In the xperiments with larger volumes the rise was much smaller and slower There was a substantial loss of applied C^1 -glucose with the stools. The loss was greater in the experiment with large than with small volumes. Glucose loss due to fermentation wa considered t play an unimportant part. The rectal beorption of 5 glucose solution was more complet and more rapid when given in small volume than when given in larger amounts. Great in dividual variations in the absorption capacity of the rectum were stressed. The sources of error associated with this method were mentioned. Rectal glucose infusions were considered of little therapeutic value Adding of hyaluronidase to the solution may improve the rectal absorption of glucose

P. Aula and *L. Hjelt*: Chromosome Studies in Human Fetuses of Spontaneous Abortions.

Research in human chromosomes has made enormous advances during the last three years. Today we know that the chromosome number in man is 46 and many chromosome aberrations have been found. The most common numeral anomaly is a trisomy which is found in connection with three autosomes and the X-chromosome; the autosomes are no. 1, 16 and 13–15. The only monosomy discovered is that of the X-chromosome. The numerical aberrations arise due to non-disjunction during meiosis or in cases of mosaicism at an early state of fetal development. On the basis of present knowledge we come to the conclusion that the X-chromosome contains less genetical material, i.e. genes, than any other chromosome because the monosomic chromosome set is not a fatal one and because the trisomy of the X-chromosome causes relatively slight disturbances. In the same way we can think that no. 21 has less genes than numbers 19 and 13–15 because a mongoloid child is far more viable than a trisomic individual of the other chromosomes. It seems probable that the trisomic and monosomic forms of other chromosomes are not viable but that they are also incapable of fertilization. There may still arise embryos with other trisomies following a non-disjunction, but because of the great imbalance of the genes they are not able to develop and the pregnancy terminates in a spontaneous abortion.

To investigate possible chromosome anomalies in spontaneous abortions, numeral or structural, a study was made on this subject. As in most other chromosome studies, the cell culture procedures were used. Two anomalous chromosome sets have been observed. The first one was a case of ovum abortivum. Only 45 chromosome could be seen in 8 cells, which could be analysed. The missing chromosome was probably from the group 16–18. The other anomalous chromosome set was seen in a four months old male fetus. The chromosome number was 46 but in 7 cells a long, dicentric chromosome could be observed. At autopsy the fetus didn't show any signs of malformations. As we know the etiology of spontaneous abortions very often remains obscure. In certain cases, a chromosome anomaly is a very probable explanation.

N. Räihä: Acid Base Balance and Organic Acids in Human Cord Blood and Amniotic Fluid

The hydrogen ion concentration, the carbon dioxide pressure, the standard bicarbonate and the base excess were studied in human cord blood and amniotic fluid with the Astrup micro equipment. The values obtained were related to the organic acids (determined enzymatically, colorimetrically and by anion exchange chromatography) in cord blood, and to the clinical picture evaluated by the Apgar score of the newborn. In cases of severe toxemia and diabetes of the mother where the newborn was asphyxiated and the cord blood showed severe acidosis the amniotic fluid had significantly lower pH and standard bicarbonat than in unasphyxiated cases. Further studies are needed in order to correlate the individual organic acids of the amniotic fluid with intrauterine asphyxia. Lactic acid and pyruvic acid in cord blood correlated with the degree of metabolic acidosis as determined by base excess. No correlation was found between the base excess of the umbilical blood and the concentration of citric, α-ketoglutaric, acetoacetic or β-hydroxybutyric acids.

J. Eklund: Fetal Hemoglobin in Hemolytic Disease of Newborn

It is generally accepted that HbF and HbA are present concomitantly in the same cell in various proportions depending on the age of the fetus or the newborn infant. About 75 % of the hemoglobin of fullterm newborn infants is fetal hemoglobin. After

birth there is a rapid decrease of the HbF content and t the age of 6 months the in fant has bout 95% adult red cells. An attempt was mad to measure the fetal hemoglobin in hemolytic disease of the new born in the postexchange period t gain information bout the bilirubin rebound. The staining of the fetal hemoglobin was performed according to the method of Betke & Kleihauer Repeated estimations of HbF reticulocytes and plasma bilirubin after the exchange transfusion did not give a correla tion between the continued destruction of erythrocytes nd the need for repeat ex change transfusion

S Koskela and *J Lusikorpi* Iontophoresis Sweat Test

(To be published in *Duodec m.*)

E. I Wallgren Nasal Eosinophilia in Asthma.

(Published in *Ann Paediat Fen* 8 278, 1962.)

Meeting June 9 1962

C. A Villee Boston: The Development of Enzyme Systems.

The properties and characteristics of each type of cell are determined by its constituent enzymes. A liver cell differs from a muscle cell, for example, not only in its morphological characteristics but also in the number and kinds of enzymes present There are both quantitative and qualitative differences in the enzyme content of the different tissues of the same individual. It has recently become apparent that the enzymes that carry out the same reaction in different tissues may differ in their molecular sizes, amino acid composition, and immunologic properties, and may show different responses to hor mones. The phosphorylases of liver and skeletal muscle for xample, have different responses t glucagon. Even in a single tissue there may be several enzymes that carry out the same reaction yet have differ ent physical and chemical properties by which they can be separated. Our recent experiments in collaboration with B Wig gert have shown that most human fetal tissues have five kinds of lactic dehydrogen ases and two kinds of malic dehydrogenases.

Advances in the field of biochemical genetics have provided reasonable hypothesis as t how biological information is transferred by deoxyribonucleic acid (DNA) from one cell t the next generation of cells in the form of code composed of the four types of deoxyribonucleotides. In each cell one or more transcriptions of the information in the form of "messenger RNA (ribonucleic acid) is made and passes out of the nucleus t the ribosomes where it provides the pattern for the synthesis of a protein containing a specific sequence of amino acids. The sequence of amino acids in the enzyme or other protein is determined by the sequence of nucleotides in messenger RNA and this in turn is determined by the sequence of nucleotides in DNA. A major unsolved problem in biology is how differ entiation of tissues is achieved—how cells with the same type of DNA, which is ensured by the process of mitosis, can undergo differentiation during embryonic development and yield cells with the widely diver gent enzymatic constit tions of the several kinds of cells in the adult The question of whether the genes simply determine the presence or bsence of an enzyme or whether they may lso determine how much enzyme there is per cell and when in the course of development the enzyme ppears, remains for future research.

Some examples of the sequential ppear ance of proteins during development were discussed Studies in collaboration with P Kelleher ha e shown that the number of immunoelectrophoretically distinct proteins in the plasma of the rat fetus increases from 5 (t 17 days gestation) to 15 (at birth). There is linear increase with time in the rat of glycolysis in the human fetal cerebral cortex

during weeks 8 to 25. The enzymes for the synthesis of glycogen appear at about 10 weeks in human fetal liver and thereafter increase rapidly in activity. The enzyme for the secretion of free glucose into the blood, glucose-6-phosphatase, appears at 10 weeks in fetal liver, at 11 weeks in fetal lung and at 14 weeks in fetal kidney. Experiments with glucose labeled in carbons 1 or 6 showed that each type of tissue has a characteristic ratio of glycolytic to pentose phosphate pathways which is established some time before eight weeks of development and which remains constant during fetal development at least to the 25th week.

The sequential appearance of enzymes for the 17-hydroxylation, 21-hydroxylation and 11 hydroxylation of the steroid ring has been demonstrated by experiments in collaboration with D. Villee. However no evidence was obtained for the presence of 3-beta-hydroxysteroid dehydrogenase, the enzyme that converts pregnenolone to progesterone, in fetal adrenals whereas there is ample evidence of its presence in the adrenals of newborn anencephalics or hydrocephalics. Perhaps the large amount of progesterone synthesized by the placenta inhibits the development of this enzyme.

The failure of any one of these enzymes to appear may lead to an "inborn error of metabolism" such as the adrenogenital virilism resulting from the absence of 21 or 11 hydroxylase, or the glycogen storage disease resulting from the absence of glucose-6-phosphatase from the liver. The several types of glycogen storage disease, each resulting from the absence of one particular enzyme, were described to show how the same clinical picture could result from the deficiency of any one of several enzymes.

Unfortunately there is no way known as yet to treat any of these "inborn errors of metabolism" by injecting the enzyme that is genetically deficient. Only a few enzymes are available in pure form, and these are from animal or microbial sources so that injecting them would lead to immunological sensitization reactions. Even if a pure enzyme were available and could be injected without causing immune reactions, it would be located in the blood and not within the cell in the particular subcellular structure where it must be to function as part of its appropriate integrated enzyme system. Furthermore any injected protein rapidly undergoes metabolic breakdown, just as do the proteins normally synthesized within the cell. It may in time become possible to "repair" the deficient gene by supplying the missing piece of DNA code and such treatments may be part of the medicine of the future.

Meeting September 12, 1962

Reports from the X International Pediatric Congress in Lisbon

Ilmari Kantero, Helsinki

The Norwegian Pediatric Society

Meeting January 26th 1962

A. Lystad and *O. Cardberg*: Quantitative Bacteriological Examinations on Children with Infections of the Urinary Tract

The main purpose of the study has been to test the value of *quantitative bacteriological* examinations in urinary tract infections in children. The authors have examined a normal material comprising 111 children (66 girls and 45 boys) presenting no symptoms of urinary tract infection and a material of 118 children (74 girls and 44 boys) with

infection. In bout 60% of the latt r cases urography revealed urinary tract anomalies and/or obstruction. In boys, specimens were obtained following thorough washing, so-called clean specimens; in girls, specimens have been partly clean" partly catheter ized. All specimens were xamined within 1 2 hours after collection using the Hoeprich quantitative method. To gauge the reliability of quantitative bacteriological analyses of "clean specimens from girls parallel exami nations of "clean and catheterized samples were carried out in 50 sample pairs from 49 girls without urinary tract infection, and in 35 sample pairs from 33 girls with clinical infection. According to Kass and other in vestigators the finding of more than 100,000 microbes per ml urine is considered a sure criterion of infection, whereas the finding of less than 10 000 microbes per ml urine is regarded as non-infection (contamination). Specimens falling between these two limits have been regarded as uncertain and new sampling has been recommended. In the normal material on was able to isolat mi crobes in about 43% of the clean speci mens from boys and 16% of the catheterized specimens from girls, mainly of the types usually found as causing urinary tract infections. The number of microbes in these speci mens was small; less than 10 000 per ml urine. From the 118 patient with infection of the urinary tract 287 specimens have been examined. Only 15 of these (about 5%) show an inverse relationship between clinical and bacteriological findings. The parallel exami nations with catheterized and 'clean" speci mens showed full agreement in 93 % of the 85 sample pairs. The practical usefulness of microscopic examination of a gram preparation of uncentrifuged urine has been confirmed. If microbes are demonstrable in every field of vision of strong magnification this corresponds to the presence in the urine of more than 100 000 bacteria per ml.

Quantitative bacteriological examinations seem t be of considerable value for differen tiation between infection and contamination. This markedly increases the value of bacteri ological examinations with sensitivity deter minations in urinary tract infections and a rational basis for medicamental antibacterial therapy is created. "Clean" specimens from girls can be employed in such examinations provided that sampling is done lege artis and that the results are critically evaluated. This voids numerous catheterizations with accompanying risk of infection.

Meeting March 30th, 1962

P F Hjort Purpura Fulminans

T Djupesland G angrenous V accinia. Hypophosphatasia

A 2-year-old boy was admitted to the Pediatric Department, Ullevål Hospital because of hypophosphatasia and gangrenous vaccinia. Both the patient and his sister have a slight degree of hypophosphatasia. The only manifestation of the disease have been premature shedding of teeth and moderat rachitic skeletal hanges. Alkaline phosphatase varied from 0 6 t 7.5 Bodansky un ts. Serum calcium and phosphorus showed nor mal values Increased excretion of phosphoryl ethanolamine was found in the urine The patient was vaccinated against smallpox in August 1961 At the sit of inoculation there developed a slowly growing ulceration which after a month was 5 by 8 cm large. There was no regional lymphadenitis. A series of bacteriological examinations of secretions from the wound showed no growth of bacteria. The patient was afebrile and in good general health. One month after vac cination treatment with immune globulin against vaccinia was instituted; 5 ml was given 3 times in the course of 6 days. Shortly after institution of the therapy the patient developed a umber of secondary vaccinia, became highly febrile and exhausted but after 10 day there were signs of amelioration. Four weeks after treatment with immune globulin had been instituted the patient had complet l recovered and the skin healed with insignificant scarring

A. B. Cyrin: Galactosemia. A Case Treated from Birth

The patient is number four of 4 siblings. Number one was born in 1954, was listless, dystrophic and icteric from birth and died at 3½ months of age. Autopsy revealed liver cirrhosis and deposits in the heart. Number two was born in 1957 and is healthy. Number three was born in 1959 and had approximately the same symptoms as number one. The diagnosis in the Pediatric Department, Oslo University Hospital was galactosemia, but the patient died with symptoms of sepsis.

Our patient was born at term. The delivery was uncomplicated. Birth weight was 3660 g. Blood sample sent t Copenhagen (Dr Brandt Dr T latrup) for determination of the galactose-l phosphate uridyl transferase showed no transferase ctivity in the erythrocytes. From birth the patient has been given a galactose-free diet: at the outset 8% dextrose 1% arobon, 6% ground rice mixture. At 3 weeks of age egg yolk was added to the diet, and at 5 weeks Velactin (Wander). The gain in weight was poor on the ground rice mixture, but improved when Velactin was given. The infant has presented no symptoms of galactosemia.

Where there is galactosemia in the family the newborn infant should be put on a galactose-free diet from birth. At the earliest opportunity the galactose-l uridyl transferase act ity in the erythrocytes should be exa ned for verification of the diagnosis.

K. Aas, P. Berdal, S. Dick Henriksen and *O. Gardborg*: On "Bacterial Allergy" in Asthmatic Children and on th Effect of Bacterial Vaccine

The role of bacterial allergy in asthma and the effect of bacterial vaccine in the treatment of asthmatic children are still discussed. The authors have only seen three investigations in which the effect of such vaccine has been tested with blind controlled placebo trials (H lander Johnstone Frankland *et al.*). None of these investigations showed signi ficant differences between the effect of the vaccine and the placebo.

At the Children Department, the Ear Nose and Throat Department, and the Bacteriological Institute of Rikshospitalet, Oslo, Norway children with presumable bacterial allergic asthma" have been followed for 12-4 months. The diagnosis is most often an exclusion diagnosis and is made when the patients have asthma prodromes and no cutaneous reaction. Following improvement in the diagnostics, the number of patients with this diagnosis has been reduced. In 1945 the diagnosis of bacterial allergic asthma was made in about 75%, in 1956 in 37% and now in less than 10%. The cause of this is the intensified testing both with cutaneous reactions and provocation tests. With such provocation tests, specific allergies were demonstrated in more than 60% of the cutaneous negative" children.

Of more than 400 asthmatic children only 28 were found who fulfilled the criteria for this study. Three of them did not come to the follow up studies, and with further retesting during the observation period specific reactions of significance for the asthma were found in 10 of the remaining 25. At the first examination there was found active rhinosinusitis in 16 of the 25 children. Pneumococci and Hemophilus influenzae were the dominating pathogenic bacteria.

On antibacterial treatment the condition of the patients improved except in two cases. Active infections in the upper respiratory tract were found during exacerbations of the allergic disease in many patients and improvement occurred following antibacterial treatment. The patients were given check up at regula intervals and vaccinations with bacterial vaccine or placebo in blind controlled pattern were given, weekly and later with increasing intervals. There was no significant difference between the effect of the vaccine and placebo. The side effects were equally distributed in the two groups. The material is too small to draw valid conclusions on the effect of bacterial vaccines. The investigation shows, however that isolated bacterial allergy—if this at all can provok asthma—is a very rare cause of asthma in children. Infections in the upper

respiratory tract are however an important factor for the asthmatic patient and optimal treatment is only achieved with a team-work between the allergist, the otologist and the bacteriologist. It is most likely that the vaccine ha small role, if at all, in the treatment and that it is the careful guidance of the patient and the parent together with the active treatment which is important for the results of the therapy

K. *Flem* Saccharase intolerance

At the Children Department Rikshospi talet, Oslo saccharose intolerance was found in a boy who had been having voluminous, thin and foamy stools since the first weeks of lif and had shown failure to thrive The diagnosis was established when he was six months old by the following investigations: flat saccharose load curve but when an invertase preparation was dded, the saccharose load ga a normal rise in blood sugar Loads with glucose lactose and mal tose were all normal. The diarrhoea stopped immediately when the patient was given a saccharose-free diet and he gained excel lently in weight. Later when small amount of cane-sugar were given, diarrhoea was promptly provoked.

M *Weln* Treatment of Fölling Disease with a Low Phenylalanine Diet

The first ttempt f dietary treatment of Föllings disease wa made by Bickel *et al.* in 1951 Since that time many patients have been treated and the best result have been achieved when treatment was started before four months of age About 30 patients of this category have shown physical and intellectual development within normal limits on dietary treatment At the Observation Home for Mental Defectives, Oslo 11 children with Fölling disease have been treated with a low phenylalanine diet during the recent three years. W have used Cymogran or Lofenalac as protein sources with low phenylalanine content A common problem on thi diet has been that the children refuse to take the food. W have had the same experience reported by other uthors: if present dermatitis disappears, the hair grow darker epileptic fit disappear and the EEG is improved. There are improvement in the degree of consciousness and the cont ct with the surroundings and there is a reduced irritability The youngest patient, who was 8 months of age when the treatment was started, is now 2½ years old and functions slightly below the normal. In older patients with signs of irreversible brain damage we have not achieved any definit improvement in the intellectual function.

Meeting Nov 23th 1962

O Aagenæs Complications in th Lower Extremities in Young Diabetics: Are They Preventable?

Literature dealing with peripheral vascular complications in young diabetics is reviewed Testing of the peripheral circulation by va rious methods during the past years has shown that poor response of peripheral vessels is an early feature of diabetes, but no definite relationship was established between duration of diabetes, its treatment or the other complications. Investigations perfor med at Steno Memorial Hospital, Gentoft Denmark, are briefly mentioned. The small peripheral arteries and skin capillaries, in biopsies from toe and finger pulp, how evidence of angiopath resembling that seen in diabetic renal and ocular lesions. Capacity of the skin vessels is examined. Legs are enclosed in separat metal boxes. Air in the boxes is cooled and skintemperature is recorded on the right and left 1st and 4th toes. On falling to 16 C, indirect heating is commenced, both arms being immersed in warm water at 43.5–44°C and heat cage is placed ver the abdomen. After latent period of 6–9 min, rat of temperature rise

to a toe temperature of 32°C is found to be average 1 9°C/min, in 40 normal persons. Diabetic material investigated includes 120 patients who developed diabetes before the age of 30 Rate of temperature rise is found to decrease along with increase in duration of diabetes, up to pproximately 20 years d ration. An insignificant normalization is noticed in temperature rise at 25 years duration and over Rate of temperature rise on the toes decreases as retinopathy becomes more severe, and at different duration of diabetes, for similar degrees of retinopathy rate of temperature rise was uniform. Rat of toe temperature rise in patients with diabetes of less than 10 years duration, and no late complications, was found t be independent of present regulation of diabetes. The material is then analysed with reference to degree of earlier diet, in patients with diabetes of more than 10 years duration, and rate of toe temperature rise in the never diet" group was significantly poorer than in the always diet" group The patients are also examined for the presence of neuropathy with special regard to the autonomic com plications, as anhydrosis, orthostatic hypotension and impotence. Incidence and sever ity of neuropathy both increased along with duration of diabetes up to approximately 20 years, whilst there were fewer cases of severe neuropathy on duration of diabetes exceeding 25 years. Anhydrosis is found in 18 cases of 89 examined the majority of patients with anhydrosis had had diabetes for 15 t 24 years, whilst no anhydrosis was found in 12 patients tested with a duration of diabetes exceeding 25 years. Fall in body temperature during cooling of the lower limbs was found to be greater in diabetics with anhydrosis than in the normal series. A higher than normal rise of body temperature during heating was also found in some diabetics, both in those whose toe temperature failed to rise, though sweating occurred on the dorsum of the foot and also especially in the group with anhydrosis on the dorsum of the foot.

S. Ozeld and *H M Stendsen*. Congenital Afibrinogenemia

Two patients, brother and sister suffering from congenital afibrinogenemia are reported. This condition has previously not been described from Scandinavia. Both suffered from severe umbilical hemorrhage soon after birth and a continuing bleeding tendency The diagnosis has been proved by coagulation tests and immunoelectrophoretic fibrinogen determinations. The hereditary nature of the disease is briefly discussed. Plasma fibrinogen estimations were made on 17 relatives but this failed to demonstrat any heterozygous carriers within the group.
(The paper will be published in *Acta Pædiat (Stockh)* *52* 1963.)

K. Halvorsen Plasma Cell Hepatitis

Plasma cell hepatitis is a chronic liver disease characterized by elevated serum proteins, especially the gammaglobulins, arthralgia and febrile periods. The disease occurs most often in young females. Liver biopsy shows post-necrotic cirrhosis with plasma cell infiltration. An 11 year-old girl who had previously been healthy was admitted to the Children Department, Ullevål Hospital, Oslo, because of hepatosplenomegaly Otherwise the physical examination was negative The sedimentation rat was 70 mm; thymol, alkaline phosphatase and SGOT were markedly elevated The serum proteins were *11.8* g/100 ml and the gammaglobulins *5.8 g/100* ml. On explorative laparatomy the liver was firm with nodules. The histological examination showed signs of post-necrotic cirrhosis with marked plasma cell infiltration. The patient was started on Prednisone and following this the sedimentation rat dropped to 16 mm, SGOT was normalized and the serum proteins fell to 8.2 *g/100* ml and the gammaglobulins to 2 0 g/100 ml This case confirms the previous experience that steroids have a remarkable effect on the pathological laboratory findings in plasma cell hepatitis. Whether or not steroid treatment affect the long-term prognosis is unknown, because the observation period on treated

patients is too short. In untreated case the mean survival is five t seven years after the symptoms occur and the longest period of steroid treatment reported is four to five years.

Sverre Halvorsen Oslo

Proceedings of the Swedish Pediatric Society

Meeting March 9 1962

Gen Carlström Vaccination against Measles.

Our family of vaccines already rather large is on the verge of being extended by another member namely measles vaccine Prophylactic treatment against measles has been considered since long ago but technical requirements for the production of vaccine have not been fulfilled until recent years. The isolation of measles virus in cultures of human kidney cells by Enders & Peebles in 1954 provided conditions for the preparation of vaccine as well as the development of serological tests for demonstrating antibodies against measles virus. Various principles have been adopted for the production of measles vaccine. Live measles virus has been employed, which has been ttenuated through numerous passages in various cell cultures. A singel injection of this virus yields full protection. This mode of vaccination has however given strong reactions (measles symptoms) It was therefore necessary to combine the vaccination with injection of gammaglobulin. Further t tempts to attenuate the virus have been without success until recently Lat ly how ever preliminary investigations in this particular field seem to permit a more opti mistic view in this respect. Vaccination has also been carried out with measles virus inactivated with formalin. No complications have been encountered with this vaccine It is, however too early to evaluat its efficacy Three injections have been given t intervals of one month. The vaccine can be combined with e.g killed polio vaccine. In Sweden vaccinations have recently been started with American killed measles vaccine.

Meeting, April 13, 1962

Symposium on *Toxoplasmosis.*

Ebba Lund, E. Lycke and *P Sourander* Toxoplasma Infection of the Cell.

Tissue-cultivated HeLa cells were infected ith Toxoplasma gondii, and the course of the infection was followed by filming with the time-lapse technique. The parasites were found again in the host cell's cytoplasm 15 minutes after inoculation. After a period of growth, first the nucleus and then the cytoplasm of the parasit divided by longitudinal binary fission. This was completed after 30–45 minutes. The first division after in oculation took 3–4 hours. Production of subsequent generations seldom exceeded one hour Each intracellular parasite produced a colony When this became sufficiently large the cell burst, and a large number of parasites, often bout 200 were liberated. These, in turn, were able to infect new cells, after which the process was repeated. This method made it possible t study the inter action of parasit and host cell. Toxoplasma is an obligatory intracellular parasit In order to study the cause of this metabolic insufficiency an experiment was carried out with radioactivated Co^{60} cells and parasites. Cells exposed t as much as 1*0,000 with

Lovisa pediatric surgery ward. Twenty-seven per cent of the children without positive findings at surgery were found to have been diagnosed as psychically disturbed preoperatively. On the other hand, only 3% of the cases with acute appendicitis were similarly diagnosed. It was also noted that parents of the former group insisted more often on surgery than those of psychically stable children. The author concludes that nervous symptoms in children may be of sufficient intensity to completely mimic the picture of an acute abdomen and lead to surgical intervention. (Published in *Z Kinderpsychiat*, 28, 210, 1961.)

Meeting Oct 12 1962

F Vassela and *B Karlsson* Asymmetric Tonic Neck Reflex—Its Presence in the Neonatal Period.

Because of controversial opinions in the literature, the question of the presence of tonic neck reflexes in the neonatal period has been restudied under standardised conditions in a series of 108 healthy neonates. The results show that the consistency with which the reflex is elicitable is an essential factor. Although asymmetric tonic neck reflex patterns were observed in 61 neonates, they could be regarded as true reflexes in only 9 neonates (=8%).

B Karlsson and *F Vassela* Labyrinthine Function in the Neonatal Period.

Observations on a newborn child with radiological evidence of bilateral severe malformation of the labyrinth and with no clinical signs of any function of these organs show that the labyrinth has a tonic action, which in this case with absent function gives a pronounced hypotonia of the neck. Furthermore some conclusions concerning the receptor of the Moro reflex might be drawn. On the nature of the receptor of the Moro reflex there are three main opinions: 1) the reflex is mediated by the semicircular canals, 2) the reflex is a vestibular reaction arising from sacculus and utriculus, 3) the reflex is mediated by proprioceptors in the neck. In the present case a complete Moro reflex was easily elicited. The findings speak against the hypothesis that the reflex is a labyrinthine reaction.

G. Wallgren, *M Barr* and *U Rudhe* Blood Pressure Homeostasis in the Newborn Infant.

Various investigators have demonstrated the presence of vaso-active material in the blood of the newborn infant and studies of the peripheral circulation have shown great capacity to changes in vascular resistance. In order to get a better knowledge regarding the effectiveness of the pressure-regulating principles in the newborn we have *studied the effect upon the circulation of* variations in the volume of circulating blood. Fifteen erythroblastotic infants were studied prior to an exchange transfusion and variations of as much as ±25% of the estimated total blood volume were stepwise induced. Blood pressures were recorded in various places in the heart and the great vessels during this alteration in the circulating blood volume.

Induced hypovolemia gave a drop in blood pressure proportional to the volume withdrawn. A reduction of 25% in the blood volume resulted in negative pressures in the great veins and the two atria and an acceleration of the pulse of 40–60 b.p.m. The systolic pressure in the right ventricle and pulmonary artery fell to 25–75% and that in the aorta to 50–65% of the initial values. Induced hypervolemia corresponding to a volume increase of 25% of the initial blood volume had no systematic effect upon the pulse rate but was followed by a rise of 10–15 mm Hg in the mean atrial pressure and of 70–110% and 25–35% of the initial systolic pressure in the right ventricle-pulmonary artery and aorta respectively.

Changes of the circulating blood volume in the newborn infant result in greater fluctuation of the blood pressure than occurs in the adult, indicating a less adaptive cardiovascular system in the newborn. The surprisingly well maintained systemic blood pressure level during initiation of breathing in the newborn, with opening up of new

vascular compartments potentially capable of creating a hypovolemic state, seems contradictory to this statement. The importance of the shift of blood from the placenta to the newborn during the very first minutes of life in the maintainance of blood pressure homeostasis is discussed and emphasized.

B. Cedergren, R. Lagercrantz and *B. Nyström*. Infections and Staphylococcus Aureus in the Maternity

Nosocomial infections probably caused by S. aureus were registered in approx. 13% of mothers and children in a maternity clinic. Twenty per cent of the mothers were nose-carriers of S. aureus on admittance to hospital and 57% on discharge 70% of the children were carriers (after 5–6 days) and 42% of the personel. Strains belonging to phagetype 80/81 were found equally often in healthy as in infected individuals. Most of the strains were sensitive to the ordinary antibiotics. The introduction of "phisohex" for hand desinfection in one ward did not influence the incidence of infections and carrier-state

Meeting, Nov 30–Dec 1 1962

A. Wallgren. Fifty Years of Swedish Peditric Society

(Will be published in *Svensk Läkartidn*, 1963.)

B. Bager, Inga Engström and *S. Kraepelien*: Sideeffects of Longterm Treatment with Corticosteroids of Children with Bronchial Asthma.

Fortysix children in different ages have been investigated with reference to linear growth and adrenal cortical function after longterm treatment with corticosteroids.—The investigation shows that the retardation in linear growth which is seen in connection with steroid treatment is correlated to the magnitude of the steroid dose given. The degree of adrenal cortex depression—measured as the amount of 17-OH-corticosteroids produced in the urine after ACTH-stimulation is also correlated to the steroid dose given. Careful supervision of these children with reference to these sideeffects is important

B. Söderling. Some Present Day Problems on Treatment of Juvenile Diabetes.

(Will be published in *Acta Paediatrica* (Stockh) 1963.)

B. Hagberg, I. Sjögren, K. Bensch and *A. M. Hedenius*. The Frequency of Infantile Hydrocephalus in Sweden.

The frequency of infantile hydrocephalus was investigated in two separat studies: the number of cases present at birth was determined in a material from an obstetric clinic, the number of cases with an onset during the first year of life was penetrated in a field study. Among all 42,547 infants delivered at the Obstetric Clinic of the University Hospital of Uppsala in 1944–61 malformations of the central nervous system were revealed in 48 cases, i.e. 1.10 per 1000 births. The corresponding figure for hydrocephalic births was 0.78. Hydrocephalus was combined with spina bifida cystica in 0.50 per 1000 births and in 0.49 per 1000 live births. In the field study made in 1961 and comprising all children born in 195_–57 in three different Swedish counties a total number of 72 cases with infantile hydrocephalus was found among 64 630 live births. "Simple" hydrocephalus was present in 55 cases, i.e. 0.85 per 1000 live births. Incomplete information was yielded regarding spina bifida cystica combined with hydrocephalus. The most reasonable value of the total number of hydrocephalic cases with an onset before one year of age was gained when the frequency figure of hydrocephalus combined with spina bifida cystica at birth was added to the frequency figure of "simple" hydrocephalus starting sometime during the first year of life. With this approximation a total frequency of 1.34 per 1000 live births was found, i.e. 22 cases

per 1 mill. inhabitants, or 14 cases of "simple" hydrocephalus and 8 cases combined with spina bifida cystica.

L. Nilsson, O Eeg-Olofsson and *R. Zetterström* Neonatal Hypoglycemia.

Hypoglycemia was the cause of convulsions in 12 of 33 neonates. The immediate perinatal history was negative as a rule in cases with neonatal hypoglycemia, while most of the others had marked intra and/or extra uterine asphyxia. The two groups also differed as regards time of onset of the convulsions. With hypoglycemia, convulsions occurred earliest on the 2nd, and generally during the 3rd, day. Convulsions of different etiology generally occurred on the first day together with other symptoms of central nervous system injury. The pathogenesis of neonatal hypoglycemia is complicated, and depends on various factors including glycogen stores, supply and consumption of glucose, enzymatic maturity and the influence of hormones such as insulin, adrenaline and glucagon. Neonatal hypoglycemia may occur with glycogen deficiency functional enzyme immaturity slow glucose breakdown, low levels of adrenaline or glucagon, hyperinsulinism, and increased glycose consumption, as in hypoxia. Often a combination of factors is present. In some cases of neonatal hypoglycemia, the ount of glycogen in muscle tissue was lyzed. A distinct tendency t lower values was found. With adrenaline loading, the initial blood sugar rise was low in comparison to tests carried out subsequently. Hypoglycemic unresponsiveness to insulin loading occurred in two cases, which did not result in raising their production of catechols when hypoglycemia was present. Hyperinsulinism was probably a factor in two or three cases. Neonatal hypoglycemia is, from a pathogenetic viewpoint, often a heterogeneous and difficult-to-investigate group but easy to diagnose if familiar with the symptoms. It is of particular importance from the standpoint of the future prognosis, in view of the risk of encephalopathy that the condition be recognized immediately and adequate treatment be given.

L. Hambraeus, C. de Verdier and *H. Boström.* A Case of Coeliac Disease Combined with Cystine-Lysinuria.

A case of a 15 month old dystrophic boy with a pathological urinary amino aciduria is described. Qualitative analysis of the urinary amino acids with paper chromatography and paper electrophoresis showed an increased output in the urine to cystine and lysine. Quantitative analyses with an automatic amino acid analyzer showed a lysine output in the urine of 350 mg per day. An examination of urinary specimens from his 18 nearest relatives, however did not show any pathological alterations in the urinary amino acid pattern.

In order to test whether the pathological lysinuria could cause the patients dystrophia, quantiative lysine analyses were performed on the patients urine after feeding two different diets, with and without the addition of lysine. There was little alteration in the lysine output in the urine if the protein content of the diet was raised 30% but if 2–3 g lysine were added per day 20–25% of it was found in the urine. The output of lysine in the urine did not seem to be of such a degree that it could give rise to a lysine deficit.

The clinical examination, including tests with xylose, glucose, and vitamine-A loads, and a histologic examination of biopsy specimen from the small intestine, showed that the patient had coeliac disease. The clinical symptoms disappeared on a glutenfree diet, but the pathological amino aciduria remained. It was not of the same type as has been described earlier in coeliac disease but of a more specific nature with a pathological lysine and cystine output

As long as the patient was in poor condition and bad nutritional stat he had a somewhat decreased output of the physiologically occurring amino acids. In a follow-up study 6 months later when the patient was in good condition and had increased in

weight the amino acid output was normal with the exception f lysine and cystine which were still pathological and in addition the output of ornithine and arginine was also increased.

The picture of the disease was thus inter preted as coeliac disease and the pathological amino aciduria was explained by the patient being a cystinuric

N O Ericsson, G. Netter and *L. Åkerrén*
Report f Preliminary Results with Combination-Treatment (Surgery X-ray-Chemotherapy) of Some Children with Malignant Tumours.

Since the treatment of childhood infections during the last decade has improved, now aday the most important cause of death in childhood are accidents and tumours. Tumour-therapy has during the last years changed completely and one has started a more intensive treatment and the prelimin ary results of this therapy have been encouraging, especially is this the case when one uses a combination-therapy of surgery radiology and chemotherapy This way of treating childhood tumours has been used by us during the last two years and w will present some views of the organisation of this treatment and give examples of typical cases. The treatment needs as other groups have shown an intensive team-work. Each patient is discussed between the surgeon, radiologist and chemotherapist. In principle the treatment primarily is surgical with extirpation, f possible of the tumour Postoperative X-ray treatment should be started very early before the wound is healed. W do not use preoperative X ray Chemotherapy for instance nitrogen-mustardtypes or actinom cins, should be given before operation and continue afterwards in combination with X-ray treatment After the initial treatment maintenance therapy is used even if no tumour or metastases are seen. The maintenance is continued for at least one year

Tw children with neuroblastoma are presented, one three months old when diagnosed, has survived 4 years with t tal regress of an inoperable tumour The other child is a boy who t the age of three weeks was operated upon but found to have large metastases of the liver Seven months after the operation he is an excellent health. Further two girls, both 6 years old, with Wilm's tumour are presented. After the primary treatment both developed pul monary metastases, which disappeared after X ray treatment and chemotherapy One of them is now years later well. The other one developed new pulmonary meta stases which this time did not respond to the previously mentioned treatment She was then reoperated with extirpation of the pulmonary metastases. Seven months later in good health.

A more intensified diagnose therapy and a *centralisation of the care of these hildren* is suggested.

B Lindquist, G Meeuwisse and *K Melin.*
Osmotic Diarrhoea in Genetically Transmitted Gl cose-Galactose Malabsorption.

Introduction (B Lindquist). The pathogenetic mechanism in diarrhoea may be of different kinds. (1) Inflammatory conditions; this is probably the most common type of diarrhoea. (2) Increased motility This group consist of i.a. so-called psychogenic diar hoea, and diarrhoea in connection with certain endocrine disorders, e.g hyper thyreosis and tumours (*ter alia* ganglioneu roma) producing substances enhancing the intestinal peristalsis. (3) Osmotic diarrhoea. The prototype is diarrhoea obtained after administration of magnesium sulfat This group also comprises generalized or selective disturbances of intestinal absorption. Finally (4) even other mechanisms, g allergy may be operating

I generalized malabsorption there is a defect re bsorption of all three main com ponent of the food f t protein and carbohydrat In coeliac disease this is the preva lent situation. Chronic diarrhoea may also be caused by selective disturbance in sugar absorption. Thus, during the last few

years, conditions of defective absorption of different disaccharides due to deficiency of different disaccharidases have been reported. At the Department of Paediatrics in Umeå we have observed a type of chronic diarrhoea due to a disturbance of the sugar absorption, not located at the disaccharide level but with a defective absorption of certain monosaccharides—glucose and galactose

This disorder may be diagnosed in the following ways: a) Measurements of the daily excretion of sugar with faeces, principally carried out in the same way as an ordinary balance study b) Sugar loading tests. After oral administration of a single dose of sugar (usually glucose, lactose, sucrose or fructose) together with a special marker (PEG) the blood sugar curve for about 3 hours and the excretion of sugar in individual portions of faeces for 1–2 days are studied.) Intubation studies. After administration of a standardized test meal consisting of *inter alia* a reference substance (PEG) the percentage absorption of different sugars in relation to each others is determined from the upper part of the intestinal tract.

Clinical and pathophysiological features (G Meeuwisse): The cases of glucose-galactose malabsorption hitherto recognized have a similar clinical history The main symptom diarrhoea, begins already after the first feedings and then increases with increasing meals. It causes a marked and ..olonged weight loss, although the infant is .. with good appetite. The frequent ..ls are of watery consistence, light yellow and sour smelling The intestinal passage time is shortened. At least in the beginning, the general condition is not impaired, but dehydration is threatening, especially if the diet consists of breast-milk only Later on the patients demonstrate the picture of severe malnutrition, unless a correct therapy is induced in time Infections and other possible causes of diarrhoea can be excluded. The condition reminds of the diarrhoic disorders due to lack of sugar-splitting enzymes. Because of the early onset lactase deficiency is most suspected. Elimination of lactose from the diet, however causes no improvement. The essential difference from disaccharide malabsorption is that in patients with the disease here reported, no disaccharide can be demonstrated in the stools after oral loadings, while on the other hand, monosaccharides are found. Loading with these monosaccharides—glucose and galactose—results in blood sugar curves as flat as after loading with lactose. Fructose loading is followed by a highly significant rise of the blood sugar level. Studies by the intestinal intubation technique show that the absorption of glucose is constantly decreased and lower than that of fructose. The therapy consists of a diet containing fructose as the sole carbohydrate. Presumably the patients are lacking a carrier substance in transport system for glucose and galactose across the intestinal mucosa. The normal transport of sugar is still mainly unknown. It is possible that the patients have the same defect in their renal tubules, because all of them demonstrate a slight renal glucosuria, which is under investigation.

Genetic viewpoints (K. Malm): Four cases of glucose-galactose malabsorption, all originating from the county of Vasterbotten, have so far been diagnosed at the Paediatric Department of Umeå hospital: three children and one adult. Two of the children are girls of 4 and 1.5 years, resp and one is a boy 6 months old. The fourth patient is woman of 35 years. A study of the familial inter relationship has shown that three of the patients are consanguineous—two of them closely—while the third is more distantly related; the relationship can be traced back to the beginning of the 18th century It has hitherto not been possible to reveal any relationship between the fourth patient and the other three, but the investigation of his family is not yet finished. The pedigree of the two closely related patient has many inbred marriages. Th..s their patients are second and third cousins, respectively Six children have died in early infancy from chronic diarrhoea in the last three generations one of these children was a sister of the four year old girl. The parents are all related

and can be traced back t the same ancestor The parents of the third patient are also second cousins. The pedigrees demonstrat an autosomal recessive inheritance of the disease.

The parents of one of the patients have been examined with oral glucose-loading tests; these were normal. Glucose-galactose malabsorption is probably an uncommon disease but in cases of resistant diarrhoea in infancy it should perhaps be kept in mind.

Kristina Berg and *O Celander* Peripheral Circulation in the Prematurely Born Infant and its Role in Control of Body Temperature.

The premature infant has often been considered handicapped by its low blood pressure a postulated poor vascularity and immature nervous control of peripheral blood vessels. The factual basis for such assumptions is meager indeed since quantitative measurements of various functions of peripheral circulation such as flow rates, pressures, resistances, maximal flow capacities and capillary filtration rates have been lacking. In a recent series of papers [Acta Paediatrica (Stockh)] plethysmographic methods to determine these functions have been described, and the same methods have now been applied on prematures. The following main conclusions may be drawn. Mean arterial blood pressure is considerably lower than in the fullterm and adult. In spite of that, the rate of regional blood flow is bout twice that of the fullterm and four times that of the adult Resistance t flow ($PRU_{mm\ ml}$) in the premature is only bout 1/8 of corresponding adult tissue That this fact corresponds to a very intense vascularity in the premature is proven by the extremely high maximal flow capacity (ml/min/100 ml,mm Hg). The capillary filtration coefficient is also correspondingly higher in the premature indicating an equal increase of the umber of circulated capillaries (but also creating certain risk for transcapillary movements of fluid in response t hydrost tic or osmotic disequilibrium). Thus the low arterial blood pressure is more than fully compensated for by this rich vascular supply permitting flow rates adequat to the rat of metabolism and a flow distribution over a rich capillary network. A lowering of ambient temperature from the neutral zone licits prompt and adequat reductions of peripheral circulation even in the very prematurely born. Parallel to this, the child often exhibits character istic motor response probably equivalent to shivering in the adult A decline in flow rates t one fourth and a motor response might well be expected upon moderate "temperature load as when ambient temperature is lowered from 32°C t 28°C. There are thus poor reasons to designat the premature as deficient or poorer in its control of body temperature compared to full term or adult standards. Obligatory heat loss promoting factors, related to the smallness, poor insulation and intense blood flow however but the premature infant in a basal situation which is very much different from that of the adult These facts should be considered in the evaluation and general care of premature infants.

B. Wengle Sulpharylating Activity of Foetal and Adult Liver

The sulphurylating activity of liver from rabbits and rats at different stages of development have been studied. Liver from rabbit foetuses (23–29 days) ppeared t have the same ability to sulphurylat p-nitrophenol as liver from adult rabbits. Studies on phenolsulphokinase the enzyme transferring sulphat from active sulphat to p-nitrophenol, showed that this enzyme was 3–4 times more potent in the liver of adult rabbit than in foetal liver Liver preparations from rat foetuses, removed on the 20th day showed no sulphurylating activity The ability of liver to sulphurylat phenol and dehydroepiandrosterone increased slowly from the day of birth to age 25 days. W th respect to last mentioned two sulphurylating activities no sex differences were demonstrable during the first 25 days

of extra-uterine life. Liver extracts from adult female rats, however sulphurylated 3–4 times more dehydroepiandrosterone than corresponding liver preparations from adult male rats. Liver preparations from human foetuses were found to have the ability to sulphurylate phenol and certain hydroxylated steroids. Of steroids tested (dehydroepiandrosterone androsterone, testosterone 17α-methyltestosterone, oestrone and 11 desoxycorticosterone) dehydroepiandrosterone and oestrone were sulphurylated to the greatest extent. Liver from a human foetus in comparison to liver from an adult showed, in general, a lower degree of sulphurylating activity. The only exception was the oestrone sulphurylating activity which did not deviate from the adult value. Human adult liver preparations were able to sulphurylate phenol, dehydroepiandrosterone androsterone testosterone, oestrone and 11-desoxycorticosterone. 17 methyltestosterone was not sulphurylated to any significant extent.

S Fällström and *J Bjure*. Hemolysis in icteric Newborns without Blood Group incompatibility

(To be published in *Acta Paediat (Stockh)* 1963.)

Kailash Agarwal and *M Michaelsson*. Coarctation of the Aorta—A clinical Study

This study is based on 68 cases, 44 with coarctation alone, 12 with associated patent ductus arteriosus (left to right shunt) and 11 with serious cardiac malformations. The latter group is not discussed. In 14 cases, left ventricular hypertrophy was present on the electrocardiogram. On cardiac catheterization, the majority showed a slight increase in pulmonary artery and PCV pressure. The distinguishing feature of the PCV curve was a prominent V wave. Forty two cases were operated on. N deaths occurred in the post-operative period. One patient died a year after surgery following angiocardiography for evaluation of an aortic aneurysm. One case had severe post operative hypertension which responded to ansolysen and reserpine. The blood pressure remained lower in the legs than in the arms in 12 of them. The optimum age for surgery is 10 years. Surgical intervention can be undertaken during the first year of life for intractable heart failure which does not respond to medical treatment.

Meeting Jan. 11 1963

Together with the Societies for Acute Infectious Diseases, Medical Microbiology and Otolaryngology

...on and Treatment of Repeated Upper Respiratory Infections in Childhood

Symposium and panel discussion. Moderator *B. Vahlquist*. Members of the panel: *G Tunevall*, *L. Philipson*, *J Ström*, *J Kinnman* and *R. Lundström*

G Tunevall, Bacterial Aetiology and Development of Immunity

As already mentioned repeated upper respiratory diseases are quite normal in children, at least during one period of life. Our subject now is the condition where the period of infections is unduly prolonged or the episodes occur too frequently. When this period occurs, how long, and how intense it is, this depends on the social status of the child and the degree of exposition thereby caused. In nursery clientele short intense and occurring during the very first years of life, it tends to be prolonged and to culminate during the first school years in children from more protected populations. Outside the big epidemics the aetiology is extremely variegated. In materials investigated in Stockholm the recovering of two or more

potentially pathogenic agents or immunologic responses against two or more such agents has been common. One virus and one or more bacterial agents have often been simultaneously involved. In the interplay of virus and bacteria thereby suggested the viral component has been considered as generally the primary one. Therefore the susceptibility of the child to viral disease is likely t influence also the frequency of bacterial infections and the development of immunity against bacteria is difficult to study as an isolated problem. This is unfortunate as the difficulty in acquiring immunity against viral disease seems to be due mainly t the manifold of immunologically unrelated viruses, against bacteria more t a comparatively weak antigenic influence.

Still, an ttempt to observe the development of immunity against the bacteria of the respiratory tract as an independent process reveals some differences between different species. The confrontation of the infant with pneumococci occurs as rule very early and results also very early in a basic immunity with a good ability of reaction, at least as far as to antipneumolysin formation. The tendency towards early relapses with the same agent also diminishes rapidly. For haemolysing streptococci the process takes place more slowly may be due to a postponed confrontation, may be because the infection tends to assume the type of the uncharacteristic streptococcal fever with faint ant body reaction. Still more slowly the process proceeds for H. influenzae the antigenicity of which is in general weak and especially so during the first years of lif. Also, the relapsing tendency is high for many years.

The immunity development may be postponed or inefficient for several reasons. Hypo- or gammaglobulinaemia will be discussed later on. Deficient resorption of antigen in superficial processes of the mucous membranes perhaps can be compensated for by the parenteral administration v vaccines. In this connection the observation of the high frequency of sinuitis (occult sinuitis") in small children, w th very good antibody response may be mentioned. Finally as will be demonstrated later on, early and effective antibiotic treatment diminishes the immunizing effect. Such treatment therefore ought to be restricted to complications as purulent otitis and pneumonia.

L. Philipson Virological Aspects

The majority of respiratory diseases ppears t be primarily caused by viruses, and bacterial infections occur as secondary complications. Several viruses within the myxovirus, adenovirus and enterovirus groups have been associated with respiratory disease. The Eaton virus has recently been established as a pleuropneumonialike organism (PPLO) and should be referred to the mycoplasma group.

Attempts to link the different viruses with a definit clinical entity have not been successful. Herpangina, caused by C xsackie A virus, and herpes blisters, caused by herpes simplex virus, are exemptions from this rule. The aetiology of the severe respiratory diseases in children, including pneumonia, bronchiolitis and nondiphtheritic croup appears to be complex. Parainfluenza virus (3 types), respiratory syncytial virus (RS) and Eaton mycoplasma are responsible for 60 % of these infections in clinical material from the U.S.A. The aetiology of mild respiratory disease in children is still unclear but an association between enteroviruses, especially the so called coryzavirus and a portion of those infections ppears likely.

Reinfection with respiratory disease viruses may occur in spit of immunological protection. This reinfection occurs less frequently than in children without antibodies and the linical picture is less severe than in the primary infection. Infection with respiratory syncytial virus might be an exemption t this rule. With regard t the high frequency of parainfluenza and respiratory syncytial virus as well as Eaton mycoplasma infections in children with respiratory disease (60 %) a polyvalent vaccin against these agents might be useful.

chemotherapy against viruses is still not possible, but some experimental results give hopes for the future

J Kinnman Prevention and Treatment of Frequent *Colds* in Children. Otological *Aspects.*

The inspired air is humidified and warmed in the nose If this respiratory organ is put out of action as by enlarged adenoids the amount of moisture becomes insufficient, the ciliary activity decreases and different agents can easily penetrate the mucous membrane. The pH of the mucous membrane is increased in allergic patients, and there is a decreased ciliary activity as well. Cooling *of the mucous membrane also gives increased* pH and decreased ciliary activity Cooling of the skin and the inspirated air decreases the temperature of the mucous membrane in the nose, and this is more pronounced in patients with frequent colds.

All these circumstances must be considered. The child has to be examined in a free interval. Allergy must be looked for specially The nature of his environment and habits as regards diets, clothing etc. inquired into Bedrooms should be properly ventilated and humidified specially during the winterseason.

If the child gets an infection he should be isolated. Nosedrops prevents complications from paranasal sinuses and ears. Antihistaminics decreases the nasal congestion during the initial stage. Infections of the nasal sinuses are uncommon before the age of two or three. Repeated sinuitis are often caused by enlarged adenoids as a result of mucous stagnation and decreased ciliary activity Enlarged adenoids are in 30% complicated with sinuitis. Adenoidectomy as a sole treatment heals the sinuitis in most cases. Treatment of the sinuitis only in the presence of enlarged adenoids gives very bad results.

The immunisation against pneumococci and Haemophilus influenzae to a great extent has its source in processes of the paranasal sinuses, and antibiotics therefore have to be reserved for the worst cases.

As a response of irritants the tonsils and adenoids will normally increase in size from the age of three months with a maximum at the age of six years. As a consequence of *frequent infections* there will be hyperplasia, which may also be produced by allergy In the presence of the wellknown signs of enlarged adenoids and its complications from ears and paranasal sinuses, the symptoms in 95% are revealed by adenoidectomy This is however not the case if the hyperplasia was caused by allergy alone. If the child continues suffering from repeated tonsillitis, often with enlarged regional lymphglands, the tonsils are themselves overwhelmed and become centers of infection. They lose their function as barriers. Chronically infected tonsils might be hyperplastic, filled by roundcells, reactioncenters, fibrous tissue and abscesses or they might be small, scarred and fibrous, adherent to the pillars, often with small, hard, regional lymphglands. This is an irreversible state and tonsillectomy has to be performed.

Rutger Lagercrantz, Stockholm.

NEW BOOKS RECEIVED

Surgery of Childhood. James J Mason Brown (Ed.). Edward Arbold Publishers Ltd., London. W L. 1962. Price 10 net.

The Well Child' Problems Management in the F rst Six Years. Gordon D Jensen. Year Book Medical Publishers, Inc. Chicago. 1962. Price 8.50.

La Mucosa Digestiva en Pediatría Carlos A. Banza and Alberto L. Matteo and Co-workers. Garcia Morales-Mercant. Montenireo. 1962.

Det Ändersæge Barn. Jacob Oster Munksgaard. Copenhagen. 1962. Price Dan. Cr 28:—

Die sogenannte Säuglingsskoliose und ihre krankengymnastische Behandlung Hans Mau und Ingeborg Gabe Georg Thieme Verlag Stuttgart. 1962. Price DM 12·80

Maternal and Child Health i the USSR World Health Organization. Geneva. 1962. Price Sw F 3 —

D fferentialdiagnose von Krankheitssymptomen bei Kindern und Jugendlichen Vol. II. *Krankheiten der Thorax und Bauchorgane.* W Catel (Ed.). Georg Thieme Verlag Stuttgart. Germany 1962. Price DM 235·—

D fferentialdiagnose seltener Lungenerkrankungen im Rontgenbild Ein Atlas. K. Mosshoff und J Weinreich. Springer Verlag Berlin-Göttingen Heidelberg 1962. Price DM 108 —

BOOK REVIEWS

Pediatri Surgery Edited by C. D Benson, W T Mustard, M. M. Ravitch, W H. Snyder and K J Welch.

Tw volumes, 1291 pages, 1004 illustrations. Yearbook Medical Publishers Inc Chicago 1962. Price $ 42 00.

I their preface the editors state: Pediatric surgery is one of the most vigorously growing fields in surgery That is obvious also from the increasing number of new text books ppearing during the last few years. This is definitely one of the very best. The editors regret that they could not enlist the services of many worth-while contributors from Australia, Scandinavia and Continental Europe It is, however more surprising that many of the most well known American names in pediatric surgery are not included in the list of contributors. Of the 79 uthors some are fairly unknown outside North America.

With so many authors the quality of the different chapters must be uneven; most however give detailed demonstration of the problems based on extensive personal experience Some statements could give rise t criticism but this does not much reduce the total impression. A whole it is very good textbook with an xcellent typography and superb illustrat ons.

N O Ericsson Stockholm

O Gárgényi Göttche. Die Tuberkulose der endothorakalen Lymphknoten im Kindesalter.

Publishing House of the Hungarian Academy of Sciences. Budapest 1962. Price DM 49.50

This is not a monograph on tuberculosis in childhood; it deals, as its title indicates, exclusively with the most common of all tuberculous diseases, that of the endothoracic lymphatic glands. Every aspect of this localisation of tuberculosis is discussed, with emphasis on lesions of the bronchial tree, compression perforation and fibrous obstruction, their pathogenesis, diagnosis and treatment. The book is based upon the personal experience of the author who is Head of the State Hospital for Tuberculous Children, but due consideration is paid to the published experience of other authors. More than 300 articles and monographs are listed in the references. There are numerous figures, mostly roentgenograms, and the text includes 90 personal case records, which add a great deal to the pleasure and profit of reading the book. The conclusions drawn and the recommendations given seem well founded and acceptable. The "Tuberculosis of the Endothoracic Lymphatic Glands in Children can be readily recommended. Its typographical appearance, excellent pape quality nice printing and satisfactory reproduction of the roentgenograms give credit to the publishers.

Töndury G Embryopathien. Über die Wirkungsweise (Infektionsweg und Pathogenese) von *Viren auf den menschlichen* Keimling V I. XI of *Pathologie und Klinik in Einzeldarstellungen.*

Springer–Verlag, Berlin–Göttingen–H idel berg, 1962 Price DM 76 —

Dr Töndury is Professor of Anatomy at th University of Zurich, Switzerland His book deals chiefly with pathological in vestigations of foetuses, the mothers of which had virus infections during early pregnancy Forty-eight mothers had rubella in the 3rd to 12th week of pregnancy and their foetuses were chiefly obtained after induced abortions. Twelve showed no abnormalities. Thirty-six foetuses were found to be damaged to some degree, the common finding being widespread endothelial and arterial necrosis. On external inspection, however the foetuses appeared normal. In 26 cases, *lens damage was found, in* nine cases brain damage, in eight cases injuries to the internal ear and in 12 cases developmental disturbances of the atrial septum. In one case, the placenta was examined. Endothelial damage led the author to suggest a haematogenous dissemination of the virus via the placenta. A few cases of virus infections of other types are also reported, viz. mumps, hepatitis, poliomyelitis and influenza. In these foetuses too, microscopical investigation revealed cellular damage t various organs. Dr Töndury investiga tions make it bvious that the role and the effect of maternal virus infections cannot be judged without careful microscopical studies of the foetuses in abortion Dr Töndury s book is beautifully illustrated and the find ings are reported in detail. However the *mass of detail makes the account unsurvey* able and difficult to read for the non pathologist.

L. Wranne, Uppsala

L. Emmett Holt J ., Rustin McIntosh and Henry L. Barnett (Ed.) Pediatrics.
13th edition. Appleton-Century-Crofts Inc., New York, 1962.

Together with 81 collaborators, among whom one finds the names of well-known North American podiatricians, the editors have managed to produce an excellent text book. "Their guiding principles were t prevent *overlapping,* to integrat the ma terial, t resolve conflicting point of view and t maintain a reasonable uniformity of style and pproach to each problem All wh *have had experience of editing* a similar multiple-author textbook are well aware f the tremendous work carried out by the three editors f this volume. The book is not to be regarded *solely as a new* edition

of the classic, H lt Pediatrics, but as a newly rewritten book. The title has been changed to *Pediatrics*, instead of Holt *Diseases of I fancy and Childhood*. Each chapter is accompanied by a very useful reference list The book is dedicated to "The Elder Statesman of American Pediatrics, Edwards A. Park"

J L. Hamerton, (Ed.): Chromosomes in Medicine.

Little Club Clinic Dev Med. 5. \ tional Spastics Society and Heinemann Medical Books, London, 1962. 232, p., 87 fig., 19 tables. Price 40s.

It is pleasure t welcome a small monograph on human cytogenetics, addressed primarily to clinicians interested in this field. It includes some brief introductory accounts of basic science written by leading authorities. Modern concepts in molecular genetics are dealt with by Symonds, normal and abnormal cell division by Harnden, classification and numbering of human chromosomes by Ford, and nuclear sex by Barr & Carr In the linical part, which makes up the bulk of the volume Polani present and discusses gonosomal aberrations, Hamerton the cytogenetics of mongolism, and Fraccaro the further autosomal anomalies so far established or supposed. The illustrations in all chapters are bundant instructive and of good quality The case material, which is in part original, is presented in easily surveyed tables. Each chapter is followed by numerous references, some of which are from the present year (1962) The monograph is warmly recommended t pediatricians and child psychiatrists.

Per Zetterquist, Stockholm

R. C Shorter Li er Biopsy An Atlas of Histologic Appearances.

Pergamon Press, Oxford, 1961 111 pp Price 60s.

Liver biopsy confront pathologist today with many problems of differential diagnosis. The morphologic base-line for structural lesions of the liver was previously drawn from experience of utopsy material. The histology of the liver at autopsy is however different from that in the biopsy owing to autolytic changes which are often marked in postmortem material, particularly in cases with severe liver damage As the biopsy is often decisive in the diagnosis of liver disease this volume is therefore welcome atlas, in many ways supplementing the comprehensive monographs already on the market. It contains a 41 page text section, 107 good photomicrographs and a bibliography of "63 references. The treatise concerns mostly liver lesions of adults, such as viral hepatitis, cirrhosis, hemochromatosis, granulomas, malignant tumors and parasitic infections. Only few pediatric problems are dealt with, namely giant-cell hepatitis, congenital atresia of the bile ducts and Wilson disease Perhaps the pediatric pathologist would have liked inclusion of the metabolic entities, such as the lipidoses, gargoylism, galactosemia and the glycogen storage diseases and a discussion of the differential diagnosis in these conditions. Also, a more detailed description of the various malignant tumors of childhood would have been interesting although the more common hepatic carcinomas of infancy are included.

The text is compact and informative sometimes a little too concise as in Wilson disease where the "hist logic appearances" are restricted to one word cirrhosis In view of the new histochemical data on the distribution of copper in the liver in hepatolenticular degeneration, such information would have been valuable in an atlas of this type The illustrations are generally of good quality The pathologist finds them informati and well selected. Presumably the linician would have benefited from a more complet description in the legends and of arrows in the photomicrographs

Dr Shorter this seems a good summary of the more common hepatic lesions n countered in a biopsy material and it should be of value to both the clinician interested.

in structural correlation and to the general pathologist.

Björn I. Ivemark, Stockholm

Praktikum der Schutzimpfung

Deutsches Grünes Kreuz, Marburg/Lahn, 1962. DM 18.50

Regulations and practice concerning immunization differ very much from country to country. These differences are not always based on differences in prevalence and severity of preventable infectious diseases. This is demonstrated once again in this German book reviewing current practice in different countries. In West Germany the immunization program is *obviously very defective*. Only 5–25% of children and adolescents are immunized against polio. The corresponding figure for the U.S.A. and Sweden is 80–90%. It is therefore not surprising to find that in 1960 3379 cases of paralytic polio were registered in West Germany as compared with nine in Sweden. Vaccination with four doses of quadruple vaccine (antigens against polio, tetanus, diphtheria and pertussis) is recommended starting at the age of four months. This is not practical in Sweden because of high levels of passively conferred antibodies recently demonstrated by B. Vahlquist and his collaborators. These German specialists recommend live ttenu vaccine, which can be given by mouth. the Canadian authorities have banned this vaccine and in the U.S.A. attenuated live vaccine type 3 may not be given to adults. In Sweden, live vaccine is used only in Salk vaccinated individuals. These specialists seem somewhat indifferent to the current problem of contamination of live vaccine with other viruses, e.g. SV 40, which can produce malignant tumors in hamsters. For a Swedish reader the strong recommendat on for immunization against pertussis is f interest as its side-effects have recently been the subject of lively discussion here. Reference is made to a WHO expert committee which came to the conclusion that severe neurological side-effects had been observed in one out of 170,000 vaccinees. The authors admit that the immunization program in Germany is very defective and a special chapter deals with the psychology of vaccination propaganda.

Rutger Lagercrantz, Stockholm

Progress in Medical Virology Ed. E. Berger and J. L. Melnick.

S. Karger, Basel/New York, 1962. SFr 54.

Medical virology is a *fast growing field*. This book contains review articles by well known workers on important problems such as lipids in animal viruses, intracellular virus with acridine orange fluorochrome, the bat as a reservoir of viruses and tumor viruses. Some of the presentation is too specialized and theoretical for those not working in the field. Many of the theories and results in these chapters, however, may soon be of great practical importance—for instance, the possibility of using lipid free virus preparations for immunization—thus probably diminishing the risk of vaccination encephalitis. *Tumor viruses which can contaminat* live polio vaccine are already a practical problem. The chapters on viral hepatitis (man is still the only virus-host who can be used for its study) and on smallpox vaccine are of more direct clinical interest. Progress is reported in the production of killed smallpox vaccine but no preparation is yet available for practical use. The result and discussions are in general of high standard and the color of tissue cultures as beautiful as some modern art.

Rutger Lagercrantz, Stockholm

Notfalltherapi bei Kindern. Pädiatrische Fortbildungskurse für die Praxis Vol. 6/7

S. Karger, Basel/New York, 1962. SF 19.—

The *rapid development* within various branches of medicine makes t necessary for the practising physician to continuously extend his knowledge in order *to* make use of recent advances within his special field.

For this purpose postgraduat courses are of great value, especially when kept at such a high level as those given in pediatrics in Berne The present book is the second part of series in which these courses are being published (in German) It contains im portant aspects of pediatric emergencies. Alarming conditions in the newborn period, the pathophysiology and treatment of cute dehydration and the differential diagnosis of acute abdominal conditions re chapters of high value. Another surgical contribution concerns burn injuries in children and is also clearly and well written. The selection of topics included in the volume may be discussed. Many important acute therapeutic problems are not dealt with, such as, e.g epileptic seizures outside the newborn period, the asthmatic attack apart for some short bronchological aspects, cardiac emergencies and accidental poisoning in childhood.

Bo Hellström, Stockholm

Reading Disability Progress and research needs i dyslexia.

Edited by John Money The Johns Hopkins Press, Baltimore, 1962. U.S. $5.

In November 1961 a conference was held at the Johns Hopkins University t which outstanding representatives in the fields of psychology psychiatry ophthalmology and pediatrics as well as in education participated. The papers given at the symposium, together with an excellent post-conference review by the editor are collected in the present volume which is indispensable for everyone interested in the topic It becomes clear from the various contributions how important it is to distinguish between various forms of congenital reading disa bility such as the "specific" dyslexia in children of normal intelligence and with no other evidence of abnormal brain function and absence of primarily disturbed emotional relations to environment, and those cases where the reading disability is only one of several symptoms indicating functional or organic disorders of the brain. The important contribution by Hallgren indicating the genetic background to "specific dyslexia is mentioned but deserved more attention in etiological discussions. Some cases of reading disability are not easy to classify and it is essential that neuropediatric aspects of the problem are not neglected. It is evident that much research is needed for a better understanding of these disorders, as is pointed out in this most valuable volume

Bo Hellström. Stockholm

ANNOUNCEMENTS

The International Children Centre in Paris will organize the following courses during 1963

In Europe:

1. Course on the dev lopment and behaviour of the child, for teachers of lementary schools (Paris, Jan. 7 F b. 17)
2. Course on school health, for physicians (Paris, Feb. 25-March 24).
3. Course of social pediatrics, for physicians (Paris, April 22-June 30).
4. Course on calcium metabolism in the child, for physicians (Paris, Sept 9-Sept. 22).
5. Course on the prevention of social malad justment for children judges (Paris, Sept 23-Oct 6).
6. Course on maternal and child welfare for

social and administrative personnel (Paris, Oct. 14–Dec. 22)

In Africa

7 Course on the prevention and treatment of tuberculosis, for physicians (4 weeks)

8. Course on school child's health, for teachers of elementary and technical schools (4 weeks).

9 Improvement course for physicians and medico-social personnel (will be held in four African republics)

In Latin America

10 Course on public health with reference to childhood problems, for physicians (4 weeks)

In Eastern Mediterranean

11 Course on public health with reference to childhood, for physicians (Beirut, 4 weeks, April–May).

In the Far East

12. Course on a subject of social pediatrics for physicians (4 weeks)

The participant holders of an International Children Centre fellowship are nominated upon the proposal of the government of their country certifying their qualifications, their knowledge of the language of the course and containing a full curriculum vitae. The candidates are expected to be sent to the Centre by the governments concerned before the date indicated.

The Second Afro-Asian Congress of Pediatrics

will be held in Jakarta, Indonesia, August 19–25 1964. Chairman: Dr Soedjono D Poesponegoro; Secretary General: Dr Sutedjo; Address: Pediatric Dept Medical School, University of Indonesia, Salemba 6, Jakarta, Indonesia.

German Congress of Pediatrics

The Nordwestdeutsche Gesellschaft für Kinderheilkunde together with the German Association for Child Care will meet in Hannover March 29–31 1963. The principal subjects to be discussed are: Current Pediatric Problems, Prognosis and Therapy of Chronic Diseases in Childhood, and Protection of the Family. President of the meeting is Prof K. N tsch, Lessingstrasse 51 Hannover Germany

LETTER TO THE EDITOR

Dear Sir

This correspondence is in reference t the article "Malignant Congenital Osteopetrosis Resulting from a Consanguineous Marriage Acta Paediatrica 51 555–558, Sept 1962, written and presented by Robert L. T ps and Henry T Lynch. During the preparation, revision and correction of the manuscript one of the authors was inadvertently omitted from the final copy. It would be appreciated if you would publish correction indicating that D C Wallace M Nott Department of Anatomy U ersity of Texas —Medical Branch is co-author of this presentation.

Thank you for your kind attention t this matter

Sincerely yours

Robert L. T ps Ph.D M.D
Chairman Genetics Department



Ivar Thorling †

$^{17}/_{11}$ 1878–$^{9}/$ 1963

Ivar Thorling died after a brief illness at the age of 84 years. It was not only age that claimed its due His only son, Head Physician to the Medical Clinic Öster sund had died suddenly and unexpectedly one week earlier No one can doubt the connexion between this event and the cardiac infarct that ended the father life

Ivar Thorling was born t Torpa Öster götland H qualified in 1900, proceeded to the degree of Doctor of Medicine in 1918 and wa appointed Reader in Prac tical Medicine at Uppsala University the same year It was perhaps more chance than design that led him into paediatrics His early training was confined entirely to general medicine For a number of years he was lecturer on this subject and for certain periods he worked at the Chest Clinic and was Consultant Physician to the privately-run Samariterhemmet Dur ing the summer he worked at one of the pas. first at the University Satra and later t Ronneby

Paediatrics in Uppsala had since 1884 had a special reader but for years teaching took place e clusively t an O t Patient Department Temporary ward were opened in 1915 and in 1924 the new

Paediatric Clinic at the University Hospital was inaugurated. Ivar Thorling had held the Chair of Paediatrics and Practical Medicine locum tenens, for four years when in 1923 he was appointed Professor in-ordinary. From 1927 the chair was in reality devoted purely to paediatrics, but the name was not changed until after Thorling's retirement.

As a paediatrician Thorling like many of his generation was essentially self taught. He used to tell how on journeys to the Continent in the 1920 s he used to be asked who had been his teacher and how he could only reply 'Myself'. His academic dissertation bore the title *Studies on the Alkaline metal Chlorides and their Antagonistic Effects*. Only a few of his supplementary papers were confined to the subject of paediatrics.

For 20 years, until 1943 Thorling was Professor and Senior Physician at the Paediatric Clinic Uppsala. Until the 1930 s this was the northernmost clinic in the country. This is striking, as today within the same region we have no fewer than 10 paediatric clinics.

Thorling was an excellent clinic chief and a first-class teacher. He was quick to recognize what was of practical importance in the care of sick children, and he was clear and straightforward in his teaching. He was authoritative, and commanded respect, but in turn always showed respect to his junior colleagues many of whom are now in charge of paediatric clinics in different parts of the country.

From an early date he was a member of the Hospital Administrative Committee and he served for 16 years on the Financial Board of the University. His excellent judgement practical bent, and command of words gave his views great import in committee meetings.

During his time as Professor Thorling was frequently seen at the Medical Association meetings on paediatrics and school hygiene. He helped to arrange the Nordic Paediatric Congresses and the 1930 International Congress in Stockholm. In the 1920 s he was called, together with Emberg to carry out the State Board of Health investigation on special training for nurses engaged in child health and sick nursing of children.

During his final year as Professor Thorling was gravely ill, and it was for a long time uncertain whether he would overcome the disease. He recovered, and for nearly 20 years he was able to enjoy otium cum dignitate. He retained his physical and intellectual capacity to the last. He followed with fervour the work of the Paediatric Clinic he took part in conferences, and he sent small gifts made with his own clever hands. Everyone loved him. His rich fund of experience and recollections and his quiet, amusing way of recounting them were entirely delightful. He was a gentleman, and a master in the art of living. Every summer he returned to the family home Holma. Meeting him in those surroundings it was easy to see the bond of union with generations of wise and cautious landholders.

Thorling belonged to an older generation of paediatricians who by dint of knowledge and ingenuity had to deal with all the problems than can arise in handling sick children. He achieved this with wisdom and good judgement. During his many years as general physician he had learnt the importance of the bedside manner and of caution in making a

pronouncement. He was not lively and spontaneous, but was thoughtful and reflective. As a family doctor he was greatly esteemed by patients of all ages.

Ivar Thorling was an Honorary Member of the Swedish Paediatric Society and of the Nordic Paediatric Association. He is mourned by numerous friends and pupils and he will be held in noble memory.

Bo Vahlquist

Acta Paediatrica 52: 231–240 May 1963

From the Department of Pediatrics, Children's Hospital, University of Göteborg, Sweden

Spirometric Studies in Normal Subjects[1]

IV Ventilatory Capacities in Healthy Children 7–17 Years of Age

by JAN BJURE

With a statistical appendix by Esbjörn Carlström

There are several reports in the literature concerning static lung volumes in healthy children, and roughly agreeing results have been reported [5, 12]. Concerning dynamic lung volumes, comparison of the results is more difficult because of differences in the apparatus employed.

It is necessary to use a spirometer with as low a resistance to respiration as possible. Bernstein *et al.* [9] have described a spirometer well suited for dynamic lung function studies in adults but in children this type of spirometer has been used very little. Few reports have appeared in the literature [18, 19] and none from the Scandinavian countries.

Using such a low resistance spirometer dynamic lung function studies have been performed on healthy children of both sexes. This paper deals with vital capacity, forced expiratory volume and maximum voluntary ventilation and their correlation to the cube of the height.

The present study is part of a larger material dealing with dynamic function studies in subjects between 7 and 70 years of age published elsewhere [1]. In this larger material both VC and FEV could be described by single equations comprising age and height as predictors.

Material

Eighty two girls and seventy-nine boys between the ages of 7 and 17 years have been studied. All children were from one school in the neighbourhood of the Hospital. The children's physical development was compared with the normal values for Swedish children given by Broman, Dahlberg & Lichtenstein [3], in which height is related to age and weight to height. In the present material only three girls and four boys fell outside the 95% confidence limits. Mean values and ranges of age, height and weight are shown in Table 1. Children with a history of lung disease and/or signs of respiratory infection were discarded from the study.

Methods

The spirometer used was slightly modified from that described by Bernstein *et al.* [2]. In this type of spirometer the flow resistance is very low, there is a small distortion of the recorded curves and it has very little recording error at respiratory

[1] Partly aided by a grant from the Faculty of Medicine, University of Göteborg. In part presented before the Swedish Association for Clinical Physiology March 11–12 1960.

TABLE 1

	Mean value	Range
Boys		
Age years	11...	7 17
Height, cm	147.0	115–179
Weight kg	40.1	20– 84
Girls		
Age years	11.7	7– 17
Height, cm	150.4	121–178
Weight, kg	41.8	20– 63

rates up to 110 respirations per minut These advantages have been achieved as follows.

(1) By making the connecting tube wide and supplying the tube with a rubber mask instead of a mouthpiece

(2) By reducing the mass of the moving parts.

(3) By increasing the cross-sectional area of the bell, thus reducing the acceleration of the bell at volume changes and thus diminishing the intraspirometric pressure changes.

(4) By modifying the water jacket, the inner annular surface area being reduced and the outer one increased, the large mass of water outside the bell thus damping the oscillations which tend t arise inside the bell.

The spirometer in this study is slightly modified in comparison with the one used in the adult materials [1]. The plexiglass bell weighed 195 g with an inner diameter of 18 cm; the connecting tube had an inner diameter of 4 cm. The volumes were recorded either by a pen ttached to the counter balance or by a ventilograph recording only the inspiratory movement of the spirometer geared down ten times, producing staircase-shaped curve at continued breathing The curves were recorded on a motor driven kymograph with three different speeds, 15, 300 and 3000 mm/min. The volume factor of the spirometer was 26.5 ml/mm and that of the ventilograph thus 265 ml/mm.

Procedure

The children were seated in front of the spirometer They were given thorough instructions and demonstrations how to per form the test and were allowed to get used t the pparatus by quiet breathing through the mask. They were instructed to press the rubber mask firmly against the face and to breathe through the wide-open mouth. Dif ferent masks were used for younger and older children. If there arose any suspicion of leakage around the mask this was held in position by the examiner who was the same for the whole material.

The terminology used is in accordance with the one accepted by British respiratory physiologists [11].

Vital Capacity (VC). The children were instructed t inspire maximally and then directly expire as deeply but not as fast as possible The best reading of at least four determinations was used. If the forced vital capacity gave higher value this one was used.

Forced Expiratory Vol me i 1 sec ($FEV_{1.0}$). After a maximal inspiration the children expired as forcibly and completely as possible Before the abrupt start of expiration the kymograph was switched over to the highest speed, 3000 mm/min. The starting point of the xpiration was determined where the first deflection occurred or at the inter section of two lines, the one drawn hori zontally at the maximal inspiration level and the other following the slope of the first fraction of the forced expiratory curve

Forced Expiratory Volume i 1 sec in percentage of Vital Capacity (FEV %) When computing FEV %, the largest $FEV_{1.0}$ and the largest VC were used, irrespective of whether the two measurements were made on the same curve or not.

Maxim m Voluntary Ventilation (MVV). The children were instructed to breathe as deeply and as quickly as possible thus choosing their own frequency MVV Special attention was paid to the breathing through the wide-open mouth. At least four and often up t 10, determinations were made and the highest one was chosen. Maximum volum

TABLE 2 *The residual standard deviations* (R.S.D.) *for all tested functions*

	Function					
	VC		FEV		MVV_F	
Predictor	Boys	Girls	Boys	Girls	Boys	Girls
Age (A)	0.581	0.482	0.411	0.421	19.87	20.14
Height (H)	0.520	0.431	0.404	0.418	21.41	15.11
Weight (W)	0.55_	0.462	0.482	0.471	22.42	18.13
H^3	0.371	0.352	0.294	0.293	19.07	14.18
A H W	0.421	0.391	0.281	0.334	19.56	15.09
A H^3 W	0.408	0.363	0.326	0.309	18.16	14.09
Log A	0.563	0.462	0.374	0.367	1.41	17.82
Log H	0.431	0.401	0.303	0.319	19.51	14.22
Log W	0.542	0.414	0.411	0.404	19.82	19.09
Log A log H log W	0.404	0.373	0.281	0.314	18.40	13.95
Total S.D.	1.1414	0.9392	0.9355	0.7335	44.02	29.56

The correlation coefficients can be obtained from the formula:

$$= \sqrt{1 - \left(\frac{\text{R.S.D}}{\text{Total S.D.}}\right)}$$

tary ventilation was also performed at fixed rates. Here the children were instructed to breathe as deeply as possible in time with a metronome at rates of 40 MVV_{40}, and 60 respirations per minute, MVV_{60}. These determinations at fixed rates were made in about 75% of the children. Readings were taken only when the rate was within ±2 respirations from the selected one. Particularly children in the lower age groups had difficulties to breathe in time with the metronome.

All lung volumes and the maximum ventilation were measured at ambient pressure and room temperature, saturated, A.T.P.S. No corrections to body temperature and pressure were made because the rapid air flow during these determinations makes it unlikely that the air will be fully saturated and warmed up to body temperature [13].

TABLE 3 *Equations for normal values and lower normal limits, residual standard deviations* (R.S.D.) *and correlation coefficients* (r)

	Mean	R.S.D.		Lower normal limit
Boys				
VC	$y = -0.1\ 5 + 0.951\ H^3$	0.37 (11.8)	0.95	$y =$ 0.004 0.779 H^3
FEV	$y = -0.011 + 0.782\ H^3$	0.29 (9.6)	0.95	y 0.009 0.591 H^3
MVV_F	$y = -9.40 + 34.64\ H^3$	19.1 (13.9 %)	0.90	y −6.78 25.14 H^3
MVV_{40}	$y = +2.30 + 22.78\ H^3$	17.1 (20.7 %)	0.90	y 2.24 16.17 H^3
MVV_{60}	$y = -7.48 + 26.13\ H^3$	16.8 (19.5)	0.96	y 5.06 19.04 H^3
Girls				
VC	$y = 0.362 + 0.736\ H^3$	0.36 (12.9)	0.92	y 0.307 + 0.591 H^3
FEV	$y = -0.221 + 0.683\ H^3$	0.30 (10.2)	0.91	y 0.167 + 0.516 H^3
MVV_F	$y = +5._1 + _8.20\ H^3$	14.2 (11.6)	0.87	$y =$ 4.03 + _2.07 H^3
MVV_{40}	$y = 15.60 + 17.60\ H^3$	10.9 (13.9 %)	0.94	$y =$ 11.26 + 1_.64 H^3
MVV_{60}	$y = +3.20 + 2.53\ H^3$	11.0 (12.2 %)	0.90	y 2.25 + 16.85 H^3

Volumes in liters ATPS, H = height in meters.

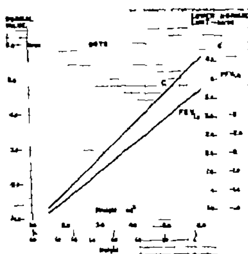


Fig. 1 Nomogram for the prediction of vital capacity (VC) and forced expiratory volume in 1 sec in percentage of vital capacity (FEV) in boys.

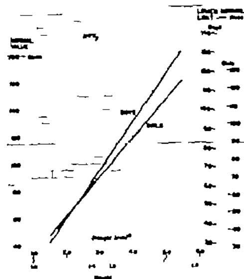


Fig. 3. Nomogram for the prediction of maximum voluntary ventilation (MVV_F) in boys and girls.

Results

The statistical procedure is described in the "statistical appendix" Of all single parameters tested, the cube of the height showed the best correlation to VC, FEV and MVV for both boys and girls (Table 2) The maximum voluntary ventilation

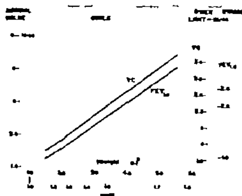


Fig 2. Nomogram for the prediction of VC and FEV in girls.

at fixed rates, MVV_{40} and MVV_{60} was only tested against the cube of the height.

There was no significant difference between the values for boys and girls taking the groups as a whole. However when comparing boys and girls 160 cm and taller a significant difference in the spirometric values was found ($P < 0.001$) Therefore girls and boys were treated separately in the st tistical procedure

In Table 3 are shown the regression equations for mean values and lower normal limit in relation to the cube of the height Nomograms have been con structed for the calculation of normal values and lower normal limit of VC nd FEV (Figs 1 and 2)

The normal range for FEV , i e the mean value ± standard deviations, wa

Mailing address for nomogram requests: Dept of Clin Physiology Sahlgrenska Jukhuset Göteborg Sweden.

TABLE 4. *Correlations between MVV_F, MVV_{40}, MVV_{60} and $FEV_{1.0}$. Regression equations, residual standard deviations* (RS.D.) *and correlation coefficients (r)*

	R.S.D	r
Boys		
MVV_F = + 2.00 + 4[illegible].94 $FEV_{1.0}$	16.7 (13.3 %)	0.91
MVV_{40} = + 2.31 + 30.41 $FEV_{1.0}$	8.4 (10.8 %)	0.83
MVV_{60} = + [illegible].34 + 31.76 FEV	11.9 (11.1 %)	0.85
Girls		
MVV_F = + 5.06 + 39.07 FEV	13.3 (9.6 %)	0.91
MVV_{40} = + 16.71 + 23.46 FEV	8.7 (12.4 %)	0.83
MVV_{60} = + 8.04 + 31.84 FEV	12.9 (13.4 %)	0.86

Volumes in liters ATPS.

85.1 % ± 11.2 for boys and 89.0 % ± 9.4 for girls. This gives a lower normal limit of 73.9 % for boys and 79.6 % for girls. The difference is statistically significant between the sexes ($P < 0.01$) and is even more significant in children with a height of 160 cm and more ($P < 0.001$).

In Fig. 3 is shown the nomogram for normal values and lower normal limit concerning MVV_F. The regression equations for MVV with fixed or free frequencies, on FEV were tested and significant correlations were found. The equations, as well as the residual standard deviations of the mean and the correlation coefficients are given in Table 4.

Discussion

Kelly first pointed out the relation between vital capacity and the cube of the height [14]. Later other authors have found the same relationship to the cube of the height [16, 18] or in logarithmic terms, approximately to the third power [4, 5]. In order to see if the logarithmic procedure affords particular merit in comparison with the cube of the height the present study was treated in both ways (cf. statistical appendix). The residual standard deviations were roughly the same. The exponents for height were very close to and statistically not different from 3 as regards VC, $FEV_{1.0}$ and MVV_F for both boys and girls (Table 6). Thus it seems of no particular merit to use the more troublesome logarithmic equations.

A comparison with other spirometric studies is difficult to evaluate, mainly because of different criteria for the selection of cases and partly because of differences in the spirometer systems used. Concerning dynamic lung function tests this latter factor is especially important, giving higher values in spirometers where the resistance to respiration is low. The lower maximum voluntary ventilations reported by other authors [6, 9, 10, 17, 20] can probably be explained by a high resistance to respiration in the systems used.

A valid comparison with other studies can only be made if the mathematical models are identical. Therefore comparisons have been confined to those using the cube or approximately the third power of the height. It is then possible to compare the regression coefficients and the

TABLE 5 *Comparison between present data and similar measurements in normal children.*

	Investigator	Sex	Prediction formula	R.S.D. (%)	r
VC	Morse *et al.* [15]	M	$y = +0.206 + 0.631\,H^3$	13	0.94
	Engström *et al.* [6]	M, F	$y = 2.97 \times 10^{-6}\,H^{[illegible]\,b}$	12.6	—
	Cook *et al.* [4]	M	$y = 0.[illegible]67 \times 10^{-6}\,H^{[illegible]\,b}$	13	0.95
		F	$y = 1.[illegible]13 \times 10^{-6}\,H^{[illegible]}$	15	0.94
	Present study	M	$y = -0.125 + 0.931\,H^3$	11.8	0.95
		F	$y = +0.342 + 0.735\,H^3$	12.9	0.93
FEV	Engström *et al.* [6]	M, F	$y = 4.83 \times 10^{-6}\,H^{[illegible]\,b}$	11.1	0.88
	Strang [17]	M, F	$y = +0.11 + 0.759\,H^3$	11.1	0.92
	Present study	M	$y = -0.011 + 0.762\,H^3$	9.6	0.95
		F	$y = +0.221 + 0.683\,H^3$	10.2	0.91

Volumes in the present study in liters ATPS, in the others in liters BTPS.
Height in meters.
b Height in centimeters.
R.S.D. (%): Residual standard deviation in per cent of mean value
r: Correlation coefficient.

exponents directly. It must be remembered that the equations in this study give values not corrected for BTPS which may be obtained, however by multiplying the volumes with a factor of 1.08–1.12. In Table 5 are given the regression equations and standard errors of the mean, given in per cent, for earlier reported studies. Concerning VC it is evident that the regression coefficients in the equation given by Morse *et al.* are approximately the same as those in the present study. It is interesting that both Cook *et al.* and Engström *et al.* have got exponents of nearly the same magnitude as here and very near the third power.

Only few studies have been reported concerning $FEV_{1.0}$. Strang using the same type of spirometer as here gives a regression coefficient quite in accordance with those found in the present study: the figures given by Strang in the equation have been recalculated to meters instead of inches. The exponent in the equation of Engström *et al.* is slightly lower probably because of the higher resistance to respiration in their spirometric system [6].

Several authors have proposed to use the $FEV_{1.0}$ value for indirect estimation of MVV_F. Strang, in his study of normal children, multiplied the $FEV_{1.0}$ values with a factor 37.5 a figure which is lower than those found in the present study for boys and girls, being 4[illegible].9 and 39.1 respectively. The correlation coefficient between MVV_F and $FEV_{1.0}$ is high and thus allows a check on the cooperation during the performance of the tests.

The values for $FEV_{1.0}$% in this study are in accordance with those reported by others [7, 15, 16]. Strang also found significantly higher values for girls than for boys.

The maximum voluntary ventilation can be performed either as a test where the child chooses its own frequency or where the frequency is fixed. In this study both techniques were used. The highest values were found for MVV_F. $MVV_{[illegible]}$ gave higher values than $MVV_{[illegible]}$. This is in accordance

with Bernstein *et al* [2], who found that the lowest optimal frequency at maximal ventilation is about 70 respirations per minute and that the ventilation increases with frequency up to at least about 100 respirations per minute. Both boys and girls in this study chose rather high frequencies, mean values 93 and 90 respirations per minute, respectively. In adult materials the standard deviation is smaller when a fixed instead of free frequency is used. Because of this and the possibility of obtaining more accurate comparison of values from one individual at different times the maximum voluntary ventilation at fixed rates has been considered more suited for clinical purposes. In the present study the residual standard deviations and correlation coefficients were roughly the same when fixed or free frequencies were used. As the children often had difficulties to breathe in time with a metronome and the test thus was more tedious and tiresome both for the examiner and the child it is advisable to use free frequency to obtain maximum results.

In previous studies concerning maximum voluntary ventilation free frequency been used exclusively. The only report with the same mathematical model is the one by Engström *et al* but as this material was examined with quite another technique no comparison between that investigation and the present one seems justified.

Summary

Vital capacity (VC) forced expiratory volume in 1 sec (FEV) and maximum voluntary ventilation (MVV) at free and fixed frequencies have been determined in normal children, 79 boys and 82 girls, 7–17 years of age. These values were found best correlated with the cube of the height. Equations and nomograms for normal values and lower normal limits are given.

TABLE 6. *The variation coefficients and the exponents in accordance with the formula*

$y = a \cdot H^b$

(H = height in meters).

		b
Boys		
VC	0.93	[illegible].80 ± 0.114
FEV	1.10	[illegible].94 ± 0.[illegible]
MVV_F	1.64	2.72 ± 0.101
Girls		
VC	1.1	2.94 ± 0.253
FEV	4.02	[illegible].88 ± 0.341
MVV_F	2.36	[illegible].84 ± 0.410

Statistical Appendix

In the statistical treatment of the material various functions have been analysed to find the "best" interrelationship between different pulmonary functions (y-variables) and one or several of the predictors (x variables) age (A) height (H) and weight (W) for the two sexes. As the "best" function was taken the one which gave the smallest residual standard deviation around the mean value. The result of this treatment appears in Table 2. However the type of function chosen was not only determined from the magnitude of the residual standard deviation since from a practical point of view a simple mathematical model is also desirable. Thus, the most suitable equation seems to express the lung function value as a function of the cube of the height according to the formula

$$y = a + b\,H^3 \qquad (1)$$

for all interrelationships.

An exception from this the FEV not presented in the table. Analysis shows that

this function cannot be regarded as a function of age, height or weight. Thus FEV % has only been given with a normal range independent of age, height and weight.

After the determination of the equation representing the mean value a lower 95% confidence limit was also calculated. The coefficient of variation was shown t vary with the x variable, being roughly directly proportional to it.

The logarithm c connections

T validat the lung function value as a function of the cube of the height the values were also studied according to the formula

$$y = \quad H^{b} \qquad (2)$$

If the two types of mathematical models express similar functions b must not differ significantly from 3. For the determination of b the following procedure has been used.

In logarithmic terms equation (*) can be expressed as

$$\log y = \log a + b \quad \log H \qquad (3)$$

Substituting in this equation $\log y = x$; $\log \quad = \quad$; $\log H = X$ the following linear function is obtained:

$$= \quad + b \quad X \qquad (4)$$

The method of the least square has been used t determine the coefficients.

The results are shown in Table 6. A t-test shows that the exponent b did not differ significantly from the hypothetical value 3 in any case ($P > 0.05$).

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Intragastric Oxygen. Experimental Observations in Newborn Puppies[1]

by L. S. JAMES[2] V. A. APGAR, F. MOYA, N. KVISSELGAARD E. D. BURNARD J. BRADY W. TUCHMAN J. S. CRAWFORD and D. A. HOLADAY

Recent studies by Coxon [2] and Cooper Smith & Pask [1] on puppies cats and kittens failed to reveal any evidence of the transfer of detectable amounts of oxygen from the gastro-intestinal tract to the systemic blood. The present experiments were undertaken to determine whether this was true also in the immediate neonatal period, before the ductus venosus and ductus arteriosus had closed

Methods and Materials

Seventeen puppies were delivered at term from three pregnant bitches, by cesarean section with the aid of nembutal and succinylcholine anesthesia. In ten, respiratory movements were prevented by administering succinylcholine (8 mg) both intramuscularly and intraperitoneally as soon as they were born. The trachea was then tied and two polyethylene tubes (Pharmaseal K 31) were passed down the pharynx into the stomach for the inflow and outflow of oxygen. Additional catheters were inserted into the aorta via the umbilical artery in six puppies, and into the portal vein within the liver via the umbilical vein in eight for serial blood sampling. These initial procedures were promptly accomplished by four individual teams, and initial blood samples obtained within the first five minutes of life.

Intragastric oxygen was administered at the rate of ½ to 1 liter per minute. After varying periods this was stopped and the lungs expanded artificially by the application of intermittent positive pressure. In several puppies the endotracheal tube was blocked and intragastric oxygen recommenced for a further period.

The remaining seven puppies were used for control observations and were allowed to breathe spontaneously. Their umbilical vessels were catheterized and serial blood samples taken both before and after administering succinylcholine intraperitoneally.

Blood samples were drawn in greased heparinized syringes for the determination of oxygen saturation percent [4]. Additional determinations of pH and CO_2 content were done using the Sanz microglass electrode [5] and the Kopp-Natelson microgasometer [3], respectively. The carbon dioxide tension (PCO_2) was obtained from the Singer & Hastings nomogram [6]. Unfortunately the deep body temperatures were not monitored so that the pH and PCO_2 values could not

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TABLE 1 *Oxygen saturation present in ten puppies apneic from birth.*

Time (in min)	Birth	Control 1–5	During intragastric oxygen 6–10	11–15	16–20	During artificial ventilation 1–20	During I.G. O_2 20–40
1	P V	8	—	15	6	74	1
	Ao	11	—	9	7	80	9
3	P V	12	—	10	7	—	—
4	P V	12		—	2	—	—
5	Ao	—	12	5	5	90	15
6	Ao	1	—	10	7	92	8
7	P V	—	—	11	2	69	—
8	P V	20	—	10	8	—	—
9	Ao	8	1	0	0	90	35
10	P V	—	—	8	7	—	—

Ao = aorta.
P V = portal vein.

be corrected for the temperature changes which undoubtedly occurred.

Results

The ten puppies which were made apneic from birth, were all profoundly anoxic by the time intragastric oxygen was started (Table 1 control samples). In the following 20 minutes there was no evidence of oxygen absorption from the stomach or gut as judged by the oxygen saturation of the portal vein or aortic blood. However when the lungs were expanded and artificial ventilation applied the oxygen levels rose rapidly (Table 1). In the second period of I.G. O_2 administration the oxygen levels again fell promptly. The fall at this time was not quite as rapid as seen in the second group of puppies which were acutely asphyxiated (Table 2). This slower rate of fall was probably related to a depressed metabolic rate as a result of severe acidosis (average pH at 20 minutes 6.6).

The pH fell and the PCO_2 rose at approximately the same rates during asphyxia (Figs. 1 and 2) irrespective of the administration of I.G. O_2. All the animals died at approximately one hour of age while receiving I.G. O_2.

Comment

These studies have demonstrated that oxygen, if absorbed from the gastrointestinal tract in the immediate neonatal period, does not reach the portal vein or aorta in detectable amounts. Further the changes which were observed in pH and PCO_2 indicate that there was a negligible

TABLE 2 *Arterial oxygen saturation in seven puppies during the first 5 min of asphyxia*

Time (in min)	0 (control)	1	2	3	4	5
1	90	39	22	—	—	8
2	83	—	—	—	9	—
3	89	—	36	—	—	6
4	92	60	—	14	—	4
5	64	1	19	—	7	—
6	76	—	12	11	—	—
7	91	—	40	—	—	1

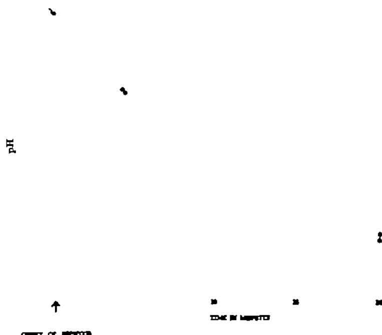


Fig. 1 Serial pH values during asphyxia in newborn puppies. ○ = receiving I.G. O_2. ● = not receiving I.G. O_2.

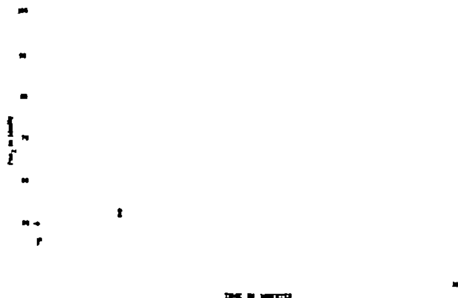


Fig. 2. Serial PCO_2 values during asphyxia in newborn puppies. ○ = receiving I.G. O_2.

exchange of CO_2 when I G O_2 was administered. The findings in these puppies therefore are similar to those in older puppies and kittens noted above [1 *]. The use of I G O_2 was completely ineffective as a resuscitation procedure even though the oxygen requirements were minimized by paralyzing the animals, and the ductus venosus, foramen ovale and ductus arteriosus were patent

Summary

Ten puppies delivered by cesarean section and paralyzed with succinylcholine were given intragastric oxygen There was no evidence of oxygen absorption from the stomach or gut as judged by the oxygen saturation of the portal vein or aortic blood. However when the lungs were expanded and artificial ventilation applied, the oxygen levels rose rapidly The pH fell and the PCO_2 rose during asphyxiation at approximately the same rate in both the experimental group and a control group irrespective of the administration of I.G O_2. The use of I.G O_2 was completely ineffective as a resuscitation procedure even though the oxygen requirements were minimized by paralyzing the animals, and the ductus venosus foramen ovale and ductus arteriosus were patent.

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Intragastric Oxygen and Resuscitation of the Newborn[1]

by L. S. JAMES[2] V A. APGAR, E. D BURNARD and F MOYA

With the technical assistance of C. Schleradl

Intragastric oxygen was first suggested as a useful technique for oxygenating newborn infants by Ylppö [9 10] Following clinical reports by Åkerrén & Fürstenberg in 1950 [1] and later Waller & Morris in 1953 [8], the method was accepted in a number of centers as ideal for newborn resuscitation primarily because of its safety and simplicity The following studies were undertaken in an effort to obtain quantitative evidence as to the effectiveness of the procedure in the human infant.

Material and Methods

Nine asphyxiated and 20 normal infants were studied. The clinical descriptions of the asphyxiated group are listed in the accompanying Table The normal infants were all mature and vigorous at birth.

Two soft polyethylene catheters (Pharmaseal K 33) for the inflow and outflow of oxygen were introduced int the stomach. Gas was administered at one liter per minut since the recommended flow rat of three to four liters per minut [1] caused the abdomen to become distended and tense Even one liter per minute proved t be too high a rate for some and in these the flow was correspondingly reduced. The oxygen content of the gas flowing from the stomach was checked from time to time with an oxygen analyser (Beckman, Model D)

Blood samples for the determination of oxygen saturation [4] were withdrawn from the portal vein, inferior vena cava or left trium by means of polyethylene catheter advanced through the umbilical vein. In some an additional catheter was passed into the aorta, via the umbilical artery and blood pressure recorded with a Statham strain gauge and a direct writing polygraph or a saline manometer

Because of the importance of maintaining the circulation t ensure maximum distribution of any oxygen bsorbed from the gastrointestinal tract and because of regurgitation of oxygen into the pharynx from where it might diffuse int the lungs, two experimental designs were adopted for the asphyxiated group. In five (Nos. 1 –, 3, 4, & 9) snugly fitting endotracheal tube was inserted and control blood samples were taken during artificial ventilation using the mouth t t be technique with oxygen-enriched pharyngeal air [6]. When the infant was pink and had a good heart beat or blood pressure intragastric oxygen (I.G O) was com-

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TABLE 1 *Data on nine asphyxiated infants*

No.	Apgar score [2]	Age after birth	Sample	Procedure	O sat. %	Arterial blood pressure	Condition of infant	Remarks
1 (ref 6)	3 at 1 min	98 min	Aorta control	IPPO	93	26 mmHg mean	Skin pink, tone good	Premature 400 g
				Endotracheal tube blocked and I G O started				Death at 2 hours of age
			Aort	I G O 2 min	24			
			Aort	I G O 5 min	6		Dark cyanosis Flaccid and motionless	Autopsy: No evidence of damage to the lung parenchyma
				IPPO recommenced				
			Aorta	IPPO 3 min	84		Skin pink, moving arms and legs	
	6 at 1 min 1 at 10 min	12 min	P V control		7	17 mmHg mean	Occasional gasps, limp, dark cyanosis	Premature 490 g
			P V	I G O 20 min Endotracheal tube inserted IPPO	7		N change	Death at 60 min of age N autopsy
			P V control		80	30 mmHg mean	Skin pink, moving arms and legs	
				Endotracheal tube blocked and I G O started				
			P V	I G O_2 10 min	10		Convulsion	
				IPPO recommenced				
			P V	$IPPO_2$ 2 min	87		Skin pink, moving arms and legs	
3	3 at 1 min	46 min	Aort control	IPPO	66		Limp, cyanotic	Premature 265 g
				Endotracheal tube blocked and I G O started				
			Aorta	I G O 11 min	3		Unchanged	No autopsy
				$IPPO_2$ recommenced				
			Aorta	IPPO 2½ min	46		Unchanged	
4	2	83 min	P V control	IPPO	76		Skin pink, tone poor Lungs non-compliant Clinical diagnosis: [illegible]	Weight 3130 g
				Endotracheal tube blocked and [illegible] started				Death at 93 min of age
							Dark cyanosis	Autopsy: Diaphragmatic [illegible]

								hernia hypoplastic lungs
				IPPO recommenced				
			P V	$IPPO_2$ 5 min	76		Skin pink	Weight: 2840 g
5	5	31 min	Aorta control	IPPO	30	65/40 mmHg	Cyanotic	Death at 2 hours of age
			Aort control	Spontaneous breathing 70% O_2	10	38/20 mmHg	Labored respiration, marked chest retraction	Autopsy: Intrauterine pneumonia due to monilia; lesions also in placenta and membranes
				I.G. O_2 started				
			P V	I.G. O 7 min	10		Steady deterioration	
6	3	20 min	P V	Spontaneous breathing 70% O	4	25/15 mmHg	Cyanotic, labored respiration, marked chest retraction	Weight: 2000 g
								Death at 1 hour of age
				I G O_2 started				
			P V	I G O 12 min	4		No change	
							Steady deterioration	Autopsy: Massive aspiration of meconium
7	—	30 hours	P V control	Spontaneous breathing 70% O_2	46	50/30 mmHg	Cyanotic, tone good, quiet respiration	Weight: 2900 g
								Death at 24 hours of age
				I.G O started				No autopsy
			P V	I.G O_2 15 min	24		No change	Clinical diagnosis tricuspid atresia (angiocardiogram)
				Spontaneous breathing continuing				
8	4	2 hours	Aorta control	Spontaneous breathing 70% O	27	32/10 mmHg	Limp and cyanotic	Weight: 2810 g
								Death at 3½ hours of age
				I G O_2 started				
				I G O_2 10 min	28			
			Aorta	Spontaneous breathing continuing				Anencephaly
			Aort	I.G O 1 hour	9	14 mmHg	Steady deterioration	
9	3	10 hours	Aorta control	IPPO	96	48/30 mmHg	Skin pink, tone poor	Weight: 2460 g
								Death at 18 hours of age
				Endotracheal tube blocked and I G O started				Anencephaly
				I.G O 4½ min		90/55 mmHg		
			Aort	I.G O 7 min	5	80/28 mmHg	Convulsions	
				IPPO started				
			Aort	IPPO 4 min	94			

$IPPO_2$ ventilation of lungs with intermittent positive pressure oxygen through an endotracheal tube.
I.G. O_2 intragastric oxygen. P V = portal vein.

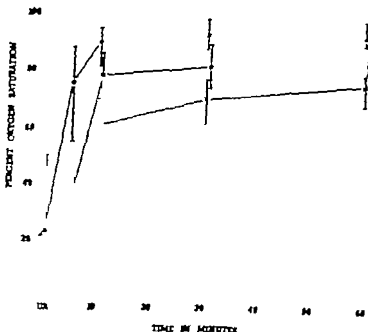


Fig. 1 Percent oxygen saturation in serial blood samples from ten vigorous infants during the first 60 minutes of lif UA = umbilical artery t birth, O = left atrium, ● portal vein, = inferior vena cava. Range is indicated by vertical lines.

menced. Once gas was flowing back satisfactorily through the outflow tube and the abdomen was distended, artificial ventilation was discontinued and the endotracheal tube occluded. In the remaining four of this group (Nos. 5, 6, 7 & 8) control blood samples were taken with the infant spontaneously breathing 70% oxygen. This environmental oxygen was maintained and the infant continued to breathe while intra gastric oxygen was administered.

In ten of the normal control group serial blood samples were taken from the portal vein, inferior vena cava and left atrium during the first 30 minutes of lif the infant breathing room air The catheter position was ascertained from the pressure tracing and the blood oxygen saturation Half of the remaining ten were given I G O from within three minutes of delivery The other half were used as controls and given intra gastric nitrous oxide

Results

Asphyxiated group (see Table I)

The five infants who were well oxygenated when the lungs were ventilated with oxygen became severely hypoxic when the endotracheal tube was occluded and I C O_2 substituted for pulmonary ventilation. They could be readily re-oxygenated when artificial ventilation was rein tituted (Nos. *1 2, 3 4 & 9*) *In the remaining four who* were breathing spontaneously (Nos 5, 6 7 8) there was no rise in oxygen level when gastro-intestinal oxygen wa given One infant (No 7) even showed a fall (48 → 34) possibly due to splinting of the diaphragm by the distended st mach.

Normal group

The percent oxygen saturation at birth and during the first 60 minutes of life in

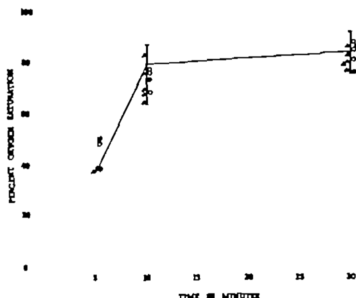


Fig 2. Percent oxygen saturation in serial portal vein samples in 20 vigorous infants. Continuous and vertical lines = mean values and range for 10 infants breathing room air. O = values for 5 infants receiving I.G. O_2. ▲ = values for 5 infants receiving intragastric nitrous oxide.

the umbilical artery portal vein inferior vena cava and left atrium are shown in Fig 1 It may be seen that the mean value in the portal vein is considerably higher than that in the inferior vena cava In some instances it was almost equal to that found in the left atrium. When the portal vein oxygen level in these infants is compared with the values found in normal infants receiving i tragastric oxygen or ntragastric nitrous oxide (Fig) it may be seen that there is no difference The infants receiving intragastric nitrous oxide remained wake and vigorous and were clinically indistinguishable from those receiving I G O_2.

Comment

These studies have shown that when the absorption of oxygen from the lungs is pathologically impaired or prevented by occlusion of an endotracheal tube absorption from the gastro-intestinal tract is negligible Failure of absorption cannot be attributed to circulatory collapse since blood pressure measurements were satisfactory and high oxygen levels were promptly achieved when pulmonary ven tilation was recommenced. The gastro-intestinal route therefore cannot be used as an alternative to the lungs for oxygena tion of the newborn.

It was of considerable interest to note that even in the previable infants ade quat blood levels of oxygen could be maintained by artificial ventilation and further that this could be achieved without apparently damaging the lung parenchyma

Relatively high levels f oxygen in the

portal vein of normal infants did at first sight raise the possibility of some added absorption of oxygen. However similar values seen in those infants receiving either intragastric oxygen or nitrous oxide indicated that this was unlikely. These high values could be explained by a lower oxygen consumption in the gastro-intestinal tissues or differences in regional circulation times.

Why then has this technique appeared to be of value from the clinical point of view? Regurgitation of 100% oxygen into the pharynx from where it could diffuse into the lungs, is one possibility. This might account for infants improving in color in the absence of visible respiratory movements. The double lumen catheter usually employed might also be acting as a pharyngeal airway holding the tongue forward in the limp depressed infant. If this were so the beneficial effects attributed to I.G. O_2 could be achieved as well by maintaining a clear airway and administering oxygen into the pharynx. Finally it is important to bear in mind that the chemo-receptors are rugged and continue to stimulate the respiratory center which responds under conditions of severe asphyxia. We have observed well-coordinated deep gasping in an infant with no measurable oxygen in the arterial blood and a pH of 6.5. This ability of the newborn to respond under conditions of severe asphyxia makes it difficult to evaluate a particular resuscitative procedure in the absence of controlled observations.

The use of intragastric oxygen is also not without danger [3]. It may reduce ventilatory movements by pressure on the diaphragm, and rupture of the stomach has been reported [7]. Perhaps the greatest danger is that it lulls the nurse or physician into a false sense of security and prevents him from thinking of, or applying effective ventilation.

Conclusion

Negligible amounts of oxygen are absorbed from the gastrointestinal tract in the human infant. High levels of oxygen observed in the portal vein of normal vigorous infants, are probably related to differences in regional oxygen consumption or circulation.

The tecnique of administering gas into the stomach is not a benign procedure and carries definite dangers. It cannot be considered of any value for resuscitation, nor as an additional source of oxygen for the sick infant. The only effective way to resuscitate a newborn infant is by pulmonary ventilation either through the infant's own efforts, or by the application of intermittent positive pressure.

Summary

The absorption of oxygen from the gastro-intestinal tract was studied in nine asphyxiated and 20 normal infants. There was no evidence of transfer of detectable amounts of oxygen from the gastro-intestinal tract to the systemic blood in the asphyxiated group when absorption from the lungs was pathologically impaired or prevented by occlusion of an endotracheal tube. High oxygen level were promptly achieved when pulmonary ventilation was instituted. Relatively high levels of oxygen in the portal venous blood of normal infant breathing room air could not be attributed to added absorption from the gut since similar values were seen when intragastric nitrou oxide wa given.

The technique of administering gas into the stomach is not a benign procedure and carries definite dangers. It cannot be considered of any value for resuscitation, nor as an additional source of oxygen for the sick infant

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Susceptibility to Infectious Disease, the Response to Active Immunization and the Antibody Titres in Diabetic Schoolchildren

by GÖRAN STERKY

The inter relationship between diabetes mellitus and infection has been much debated and no clear picture is yet available [10 36]. In the past infectious diseases especially pulmonary tuberculosis, contributed to a large proportion of diabetic deaths [36 50], but the advances of recent times, e.g. higher standard of living, antibiotics, have naturally altered this situation a great deal. And yet today opinions still differ as to whether diabetic patients have a normal or increased susceptibility to infection. Recent text books [15 36] sum up earlier studies in statements supporting the view of low resistance to infectious disease in the diabetics, at least in the poorly controlled. As regards children and adolescents with diabetes hardly any information based on controlled investigations is available in these respects.

In studying different factors of prognostic significance in juvenile diabetes, a material was assembled which, with certain supplementary arrangements, could also be used for an investigation of the children's mode of reaction in infectious disease. This paper deals with a clinical and sero-bacteriological study on a group of diabetic schoolchildren and matched non diabetic controls.

Material and Methods

All diabetic children attending schools in Stockholm during the school year 1959–1960 were registered. A non-diabetic control was selected for each of them according to the social twin principle. For different reasons (untraceability and unwillingness) the final groups comprised 145 diabetics (87.9 %) and 126 non-diabetics (81.3 %) of which 238 were matched into pairs. The children in a matched pair belonged to the same sex and class at school and were similar as regards age, social group, dwelling standard and number of siblings [53]. The number of cases studied in the different aspects is to be found in the figures and tables. The variation in the number of participants could not be attributed to any special cause and the figures may therefore be regarded as non-selective. The material was divided into five age groups 7–10, 11–12, 13–14, 15–16 and 17–20 years. Only very few cases, however, were as young as 7 or older than 18 years. The social grouping corresponded with that generally met with in Stockholm [53]. The mean duration of diabetes was 4.8 years (range 8 months–16 years) and 43.3 % of all diabetics were classified as of "poor" control [52, 53]. The therapeutic principles followed at Crown Princess Lovisa's Children's Hospital on 42.2 % of the diabetics in the present material have been described previously [30].

The intention of the study was to follow the two groups during the school year 1960–1961. During the spring of 1960 all families

concerned were given information about the investigation by letter and telephone by the author and the assisting nurse. Over a two-week period in September 1960 and again in February 1961 all children were called to the hospital for physical examination and blood sampling, including determination of the erythrocyte sedimentation rate (ESR, Westergren method.) The children were requested to appear on both these occasions only if they were subjectively free from infectious disease. The mothers were instructed to report every incidence of illness in their children, even the slightest signs or symptoms. The assisting nurse was in continuous telephone contact with the mothers who were furthermore reminded of the investigation from time to time by letter. When falling ill only a few of the subjects, however, could be attended by the author in person.

During a personal interview with the mothers at the end of the observation period in May 1961 it was possible to check the reports given during the previous months as regards frequency and types of infectious diseases. The information obtained corresponded well with our annotations. The history as regards the common epidemic diseases of childhood was recorded, as well as information concerning otitis media, adenoidectomy and allergic disorders (asthma, rhinitis and eczema). The anamnestic data were too unreliable to permit us to distinguish between illnesses occurring before or after the onset of diabetes. The mothers were also asked to classify the frequency of acute infectious diseases during the year of study in three classes: seldom, once a month, or more than once a month. After completion of the study the school attendance sheets were reviewed and the number of absentee hours or days noted. Due to differences in the form of registration in the various schools only matched pairs were analysed in this way.

In recording the incidence of acute infectious disease many difficulties were met with. In order not to over- or underestimate the frequency the following procedure was applied. Included in the group of acute respiratory diseases were those with local as well as general symptoms. As could be expected, many children suffered gastrointestinal disturbances in the course of an infection beginning in the upper respiratory tract and these conditions are therefore treated under the heading of acute infectious disease. Clearly with illnesses of this nature it is often difficult to know whether a child has suffered from a sequence of different illnesses or from exacerbation of the same one, and whether this, again, has been due to the same etiological agent or to secondary infection. When evaluating the data it was decided to restrict incidence to one recording per month per child. The degree of severity or the duration of each illness could not be assessed.

In February 1961 pharyngeal and nasopharyngeal swabs were taken, immediately placed in tubes containing Stuart medium and stored at 4°C. The swabs were cultured on the following morning and potentially pathogenic bacteria verified according to conventional methods. Only bacteria found in direct smear culture on solid media are reported. As acutely ill children did not take part, the findings represent "healthy carriers" alone.

In May 1961 all children were invited to take part in a typhoid/paratyphoid vaccination programme. The antigen employed was the ordinary vaccine produced at the Swedish National Bacteriological Laboratory. This preparation contains about 2 billion bacteria per ml (*Salmonella typhi* 50 %, *S. paratyphi* B 25 % and *S. paratyphi* A and C 12.5 % each). 0.25 ml was given subcutaneously to each subject. Blood samples were obtained before the vaccination as well as 10 and 20 days afterwards. Since it was impossible to manage more frequent sampling, only one injection of the vaccine was given in order to prevent the possible distortion of the results by booster effects.

Blood samples were taken by venipuncture in sterile glass tubes with screw caps. The blood was allowed to clot at room temperature, the serum separated off and stored in

TABLE 1 *Anamnestic data*

Figures in brackets denote number of cases where complete information was available

	Diabetics				Non-diabetics			
	Boys (67)	Girls (76)	Total (143)		Boys (60)	Girls (66)	Total (126)	
Condition	n	n	n	%	n	n	n	%
Pertussis	31	50	81	56.6	31	43	74	58.7
Measles	55	63	118	82.5	44	63	109	86.5
Chickenpox	51	63	114	79.7	44	51	95	75.4
Rubella	[illegible]	37	58	40.6	18	[illegible]	49	39.1
Mumps	33	41	74	51.7	32	39	71	56.3
Scarlet fever	13	14	[illegible]	18.2	7	7	14	11.1
Otitis media	20	27	47	32.9	16	17	33	[illegible]
Adenoidectomy	13	14	27	18.9	19	12	31	24.6
Allergic disorders	4	6	10	7.0	6	9	15	11.9

the frozen state until analyzed. When sufficient sera had been obtained the titres of all three of the following antibodies were determined: antistreptolysin AS; [25], antistaphylolysin, ASta; [42] and antipneumolysin, APn, [57]. The Widal test was performed on sera from the vaccination study and if the sample sufficed, an assay of the above antilysin titres also. All samples from both of the children in a matched pair were always assayed together in order to eliminate variation in the test system.

If not otherwise stated, the statistical treatment was performed according to the χ^2 method

Results

The data obtained from case histories are listed in Table 1 There is a good correspondence in the frequency of various disorders between the two groups. The greatest difference is found for scarlet fever but the numerically higher incidence among the diabetics is insignificant ($P <$ 0.2). Analysis in respect of age revealed no differences between diabetics and non-diabetics. A number of other infectious diseases had also occurred in both groups but their frequencies were too small to permit statistical assessment.

In Table 2 the frequency distribution of the number of absentee days is compared in the matched pairs in which the children remained classmates during the school year of study The mean number of days of absence per child and year was 22.1 in the diabetic and 13.8 in the non-diabetic group Age had no pronounced influence but 40 diabetics of "fair" control had a mean absence of 19.9 days as opposed to a mean absence of 23.0 for 32 grouped as of "poor" control ($t = 1.3$, p 0.%). In the matched pairs the higher absenteeism among the diabetics was of the same magnitude in both sexes and during both school terms of study In 73 % of the pairs the diabetic was absent from school for a longer period than the paired classmate On sign test this difference was found to be highly significant (p 0.001) The number of days of absence during the school year 19.8 1959 displayed the same differences as for the year of study

TABLE 2. *Number of days of absence during the school year 1960–61 in 74 matched pairs*

No. of days of absence	Diabetics Boys n	Girls n	Total n	Total %	Non-diabetics Boys	Girls n	Total n	Total %
0– 9	9	9	18	24.3	16	17	33	44.6
10–19	12	9	21	28.4	15	10	25	33.8
20–29	6	6	12	16.2	5	5	10	13.5
30–49	9	7	16	21.6	2	4	6	8.1
> 50	2	5	7	9.5	—	—	—	—
Total	38	36	74	100.0	38	36	4	100.0

(89 pairs, mean absence $D = 22.5$ days, $V = 12.9$ days 79 1 %, $p < 0.001$)

At the interview the mothers reported 8 (11.9 %) diabetic boys and 9 (11 8 %) diabetic girls to have suffered from acute infectious disease once, or more each month. Corresponding figures for the non-diabetic group were 5 (8.2 %) and 8 (12.1 %) There were * cases in the diabetic and 3 in the non-diabetic group where the mothers reported more frequent illnesses than had previously been recorded.

A few cases of epidemic disease occurred during the period of observation (Table 3) No intra pair difference could be seen. The incidence is numerically somewhat higher for the diabetics but the number is too small to allow any conclusions

The incidence of acute infectious disease is given in Tables 4 and 5 and Fig. 1 The total number of "infections" is significantly higher among the diabetics than among the non-diabetics ($p < 0$ 001). The number of infectious diseases per case and period of observation is higher among boys in both groups (Table 4) All age groups show a declining frequency with advancing age (Fig 1) and the higher morbidity among diabetics disappears in the two oldest age groups The diabetics

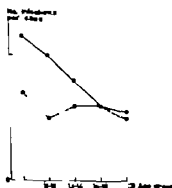


Fig 1 Mean incidence of acute infectious diseases per case in the various age groups during the period of observation. (No. of cases is given in Table 4) ●——● diabetics, ○ non diabetics.

TABLE 3 *Incidence of certain epidemic diseases during the period of observation*

Diagnosis	Diabetics Boys	Girls	Non-diabetics Boys	Girls
Pertussis	1	1	—	—
Measles		4	2	1
Chickenpox	—		1	—
Rubell	1	1	4	2
Mumps	3	3	2	—
Total	7	11	9	3

TABLE 4 *Incidence of acute infectious disease in relation to age and sex*

Figures in brackets denote number of cases.

	Diabetics						Non-diabetics					
	Boys			Girls			Boys			Girls		
Age group	"Infections" *n*	"Infections per case		"Infections" *n*	"Infections per case		"Infections" *n*	Infections per case		"Infections" *n*	Infections per case	
7–10	40	[illegible]	(17)	[illegible]	2.3	(16)	22	1.8	(15)	16	[illegible]	(13)
11–13	25	[illegible]	(11)	1	1.8	(12)	7	0.7	(10)	14	[illegible]	(12)
13–14	32	1.8	(18)	23	1.4	(16)	19	1.3	(16)	17	1.2	(14)
15–16	20	1.8	(11)	19	0.9	([illegible])	13	1.6	(8)	[illegible]	1.1	(18)
[illegible]–20	8	0.8	(10)	15	1.4	(11)	14	1.3	(11)	4	0.8	(5)
Total	126	1.9	(67)	[illegible]	1.8	(78)	75	1.3	(60)	71	1.1	(64)

differ especially from the non-diabetics in displaying lower frequency of cases without any illness and also in displaying a greater number with frequent incidence (Table 5). The occurrence of infectious disease could not be connected with social group, crowding in the home or with the degree of diabetic control. Among the diabetics there were 3 cases of urinary infection, 3 of dental and 9 of skin infection, severe enough to need medical treatment. Among the non-diabetics the corresponding figures were 1, 0 and 1.

The bacteriological isolations from pharyngeal and/or naso-pharyngeal swabs are indicated in Table 6. Potentially pathogenic bacteria were found more often among the diabetics than among the non-diabetics ($p < 0.02$). As regards the individual types of bacteria no significant differences were found (the difference was greatest for β-streptococci ($p < 0.1$)). No age distinction was observed.

The mean value of all recorded antibody titres was calculated for each case and, when two or more serum samples had been tested the "range" within which the titres had varied during the observation time, i.e. the quotient of the highest and lowest titre observed. All three anti-

TABLE 5 *Distribution of cases with varying incidence of acute infectious disease*

	Diabetics				Non-diabetics			
No. of "Infections	Boys *n*	Girl *n*	Total		Boys	Girls	Total	
0	13	1	34	23.4	18	27	45	[illegible]
1	19	23	[illegible]	[illegible]	21	19	40	31.7
2	13	16	[illegible]	20.0	11	9	[illegible]	18.9
3	10	11	[illegible]	14.5	8	10	[illegible]	14.3
4	9	5	14	9.7	2	1	3	[illegible]
5 or 6	3		5	3.4	—	—	—	—
Total	[illegible]	8	145	100.0	80	66	[illegible]	100.

TABLE 6. *Combined results of bacteriological cultures from pharyngeal and nasopharyngeal swabs.*

Figures in brackets denote total number of cases. From 8 diabetics and 5 non-diabetics two different species were recovered.

	Diabetics				Non-diabetics			
	Boys (63)	Girls (67)	(130)		Boys (60)	Girls (65)	(125)	
	n	n	n	%	n	n	n	%
β-streptococci	7	6	13	10.0	1	4	5	4.0
Staph. aureus	13	13	26	20.0	11	5	16	12.8
Pneumococci	4	6	10	7.7	5	3	8	6.4
H. influenzae	4	3	7	5.4	3	3	6	4.8
Total	28	28	56	43.1	20	15	35	28.0

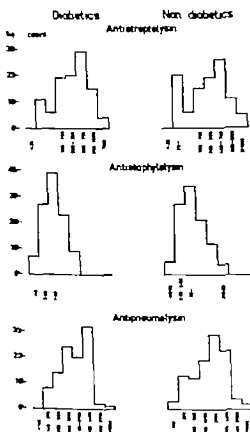


Fig. 2. Distribution of the individual means of antibody titers (IU/ml) in 103 diabetics and 104 non-diabetics.

lysin reactions were performed in 103 diabetic and 104 non-diabetic children. The average number of sera per subject was 3.5 for the diabetics and 3.7 for the non-diabetics. The distribution of the mean antibody titres is given in Fig * which indicates a general correspondence between the various antilysins in the two groups. The "range" of the titre changes was about the same at different levels of mean titres and that of the diabetics did not deviate from that of the non-diabetics. A greater than twofold change in the antibody titre was found as frequently in both groups (Table 7). The averages of the individual means were also correlated to the degree of diabetic control without revealing any differences for any of the titres. In the youngest age group the diabetic children had a higher average for the mean level of AS (Fig 3) and APn than corresponding non-diabetics. In the matched pairs the frequencies of very low individual titre values were analysed after dividing the materials at different levels (T ble 8). The diabetics had fewer AS-values <25 less APn-values <290 but a higher frequency of ASta titres <0.5 In

TABLE 7 *Greater than twofold change in antibody titres during the whole period of observation in 103 diabetics and 104 nondiabetics.*

	Diabetics				Non-diabetics			
	Boys	Girls	Total		Boys	Girls	Total	
	n	n	n	%	n	n		%
AS	22	18	40	33.8	15	18	33	31.7
ASta	3	4	7	6.8	5	3	8	7.7
APn	19	28	47	45.6	18	34	52	50.0

the youngest age group (7–10 years) the frequency of individual AS ≤ 200 was 41.9 % among the diabetics and 84.2 % among the non-diabetics ($p < 0.001$)

The distributions of the erythrocyte sedimentation rates from the two samplings are given in Table 9.[1] The diabetics have a higher frequency of slightly elevated ESRs in both samplings. The differences between the September values for the diabetics contra the non-diabetics is probably significant ($p < 0.02$). The results of the two samplings differ for all categories in showing a higher incidence of elevated ESRs in September. There is a probably significant difference ($p < 0.05$) between the frequencies among the diabetics for these two months.

[1] A few additional diabetics had an ESR of ≥ 21 mm/h (3 cases in September and 2 cases in February). They are omitted in the table as they showed obvious signs of acut illness and thus did not fulfil the requirements of selection.

As "infected" cases were omitted the possibility of correlating different observations was diminished. In the cases in which potentially pathogenic bacteria were isolated (Table 6) the extent of greater than twofold titre increase which had occurred

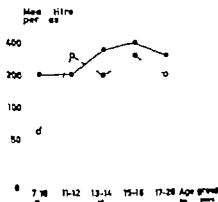


Fig. 2. Average age-group values of the individual means of AS in the matched pairs. ●——● diabetics; ○– – –○ non-diabetics.

TABLE 8 *Frequency of low individual titres in the matched pairs.*

Figures in brackets denote total number of sera.

	Diabetics		Non-diabetics		Probability of diff.
	n	[illegible]	n	[illegible]	
AS < 25	20	7.6 (262)	6[illegible]	21.5 (288)	p 0.001
ASta < 0.5	[illegible]6	[illegible].4 (261)	43	18. (233)	p 0.01
APn < [illegible]0	22	8.0 (2[illegible]4)	4	14.9 (292)	p 0.03

TABLE 9 *Distribution of ESRs in September 1960 and February 1961*

	Diabetics				Non-diabetics			
	Boys	Girls	Total		Boys	Girls	Total	
ESR, mm/h	n	n	n	%	n	n	n	%
September								
0–10	48	47	95	75.4	52	56	108	87.8
11–20	11	20	31	24.6	6	9	15	12.2
Total	59	67	126	100.0	58	65	123	100.0
February								
0–10	34	29	63	87.5	39	39	78	90.7
11–20	4	5	9	12.5	4	4	8	9.3
Total	38	34	72	100.0	43	43	86	100.0

from February to May was investigated. However only in single cases could any connection be established. The distribution of antibody titres in relation to the ESRs from the sampling in September is given in Table 10. No differences were found between diabetics and non-diabetics and the frequency of pathological titres was not significantly influenced by the small increases in ESR. Positive bacteriological cultures were found as often in cases with ESR 0–10 as in those with ESR 11–20. The frequency of greater than twofold titre changes from September to February or from February to May was the same irrespective of diabetes or level of ESR.

The agglutination titres to *S. typhi* H antigen are given in Fig. 4 in the form of cumulative frequency diagrams. The findings for the various groups are very similar and there was furthermore the same number of cases in both groups showing titre changes between the two occasions of blood sampling. Only in single cases, to the same extent in both groups, was there an antibody response to

TABLE 10. *Frequency of pathological titres (AS > 200, ASta > 1.4 and APn > 400) in relation to the ESR*

	Diabetics				Non Diabetics			
ESR mm/h	0–10		11–20		0–10		11–20	
No. of cases	90		28		94		15	
	n	%	n		n	%	n	%
AS elevated	69	76.7	20	71.4	63	67.0	10	66.7
ASta elevated	31	34.4	14	50.0	43	45.7	8	53.3
APn elevated	84	93.3	26	92.9	88	93.6	13	86.7
Two titres elevated	48	53.3	11	39.3	48	51.1	6	40.0
All titres elevated	23	25.6	10	35.7	30	31.9	5	33.3



Fig. 4. Typhoid/paratyphoid immunization. Agglutination titres to *S. typhi* H shown in cumulative frequency curves. ——— diabetics, ‐ ‐ ‐ ‐ non-diabetics. No. of subjects examined After 10 days: D 55; N 60. After 20 days: D 59; N 69

other antigens than *S. typhi* H. Neither age nor degree of diabetic control influenced the antibody response. Subjective and objective side effects to the vaccination such as fever and pain were few and as frequent in diabetics as in non-diabetics. The experiences of the diabetics were in fact so good that most of them accepted the second vaccine dose offered. On only 5 occasions (about 3 % of injections given) was such an influence on the diabetic state reported as demanding extra measures.

Discussion

The material used in this study was assembled to throw light on various aspects of diabetes mellitus in childhood and adolescence. For most of the separate studies in the series of investigations performed on this material it was necessary to examine the children when they were free from any form of acute infection. When studying immunological response this is of course a drawback, as also the limited possibility of supervising the children and collecting blood samples and swabs in connection with acute illnesses. However, it was considered worthwhile to attempt a survey of various circumstances connected with susceptibility to infectious disease in diabetes.

It might have been expected that the parents of the diabetic child would have had more interest in this investigation than those of the non-diabetic, but the author was not given the impression of obtaining less accurate information from any group of parents. As in similar studies in Stockholm [*1] cooperation proved easy to establish with the parents and they seemed to appreciate the advantage of being offered ready advice about the children's health without having to pay for it. The observation of a higher incidence of infection disease among boys than among girls and the declining rate with advancing age tallies with the findings of others [–, 60] and speaks in favour of the reliability of registration.

The definition of illness, especially in the field of respiratory disease, and the question of "new" illness or the progression of an old one have been the subject of

much discussion [2, 18, 21 38]. Every set of criteria will lead to some misinterpretation of the facts [ ] and this, together with variation in definitions, must prevent the valid comparison of different studies.

The diabetics in this material had an increased incidence of episodes of illness (Table 4) and the number of days of absence was higher (Table 2) when compared with the non-diabetics. No comparable figures have been found elsewhere but some information is available for adult diabetic employees. Thus a higher rate of sickness absenteeism has been found among diabetic workers than among comparable non-diabetics [6, 43] In their well-documented study on 408 diabetic employees Pell & d Alonzo [43] found no increase in the incidence of absence due to respiratory infections or diseases of the digestive system. On the other hand it was observed that after the onset of disability the non-diabetics returned to work earlier In the present material (Tables 2 5) it seems as if the greater absenteeism and higher frequency of infectious disease among the diabetics is confined to a limited number of cases. This observation tallies with that of others [3 29 43]. The diabetics grouped under "poor" control had a somewhat higher mean number of days of absence than those under fair" control.

It was impossible to decide whether the diabetics suffered from severer types of illness or if one and the same type had led to a voluntary longer stay at home by the child with diabetes than by his non-diabetic fellow Diabetic patients have a greater need of insulin during illness [15 36] The causes are not fully known but circulating insulin ant gonists, increased adrenal activity and other factors have been considered [8 10 13 16]. However adequate regulation of diabetes during acute infectious disease demands special precautions, one of which is to give a diabetic child a somewhat longer time at home to recover after an acute infection. There is good reason to believe that this rule is commonly observed and, if this holds true, the minor differences observed between diabetics and non-diabetics as to the incidence of acute respiratory disease and the distribution of the various anti lysin titres could be given an at least tentative explanation.

The special protection of diabetic preschool children in connection with acute respiratory illnesses most likely to be primarily caused by viruses [2, 27 56], may diminish the risk of bacterial super infection to which they have been supposed to be especially liable during such a period [60]. Therefore when entering school, the diabetic child may lag behind its non diabetic classmates with regard to the immunizing effects of sustained bacterial diseases This lag may not be overcome until the teens.

The lower incidence of very low (≤.5) AS among the diabetics may thus suggest that there are fewer such subjects who have escaped streptococcal infection for a time as long as to allow a reversion to really low AS values For the 7-10-year group, where this tendency should be more pronounced than among older children [50] the above observation is also supporter by a high incidence of acute respiratory illness, of scarlet fever and by a higher carrier rate of β-streptococci, as well as a significantly lower incidence of AS titres below 200 The very low incidence of really low APn titres in the

diabetic group may be interpreted in the same way

On the other hand, the diabetics had a higher frequency of very low ASta titres In keeping with the above line of argument the explanation of this should be a lower rate of staphylococcal infections among the diabetics, due to a diminished exposure or to a higher resistance. This, however appears improbable. The diabetics were somewhat more often carriers of staphylococci than the non-diabetics [cf. 58] and they also had more frequent infectious conditions (e g skin infections) often known to be caused by staphylococci The possibility therefore remains that some diabetic children have a low ability to form antibodies staphylococci [cf 3]

As may be seen from Fig 2 there was a good correspondence in the distribution of the averages of the various antilysin titres in the two groups. The titre changes both the 'range' and the frequency of greater than twofold change during the year were of the same magnitude in the diabetic as the non-diabetic group (Table 7) This implies no major impairment of the diabetics ability to react with the formation of antibodies to common bacteria.

The active immunization was undertaken in order to exert a constant antigenic stimulus on all children. The typhoid/paratyphoid vaccine was chosen as containing different antigens to which the children had not previously been immunized and of which they would have some benefit There were no increased side effects to the vaccination among the diabetics, and the diabetic state in itself should probably not be regarded as a contradiction to active immunization. A response to *S typhi* H antigen was generally found and results were strikingly similar in both groups (Fig 4) Active immunization has been employed by many investigators both on experimental animals [48] and clinical material [40 4]. A decreased or delayed antibody formation in connection with typhoid vaccination in adult diabetic patients [40 47] and to staphylococcus toxoid in diabetic children [3] has been shown. Variations may be found in the response to different types of antigenic stimulation and the antibody titres provoked by certain bacterial antigens in the present study cannot with certainty be taken as being representative of the over-all antibody potential of the patient.

During periods more or less free from epidemics the etiologic agents in acute respiratory illness seem to be very complex [50] and even very intense investigations of closed communities have failed to reveal the etiology of more than a limited proportion of observed illnesses [*]. During the period of observation of this study no major epidemics occurred among the inhabitants of Stockholm and consequently there was no known infectious agent bacteria or virus, which was as widely spread and potent as to provoke antibody titres to such an extent that differences between the two groups might have been observed. It was therefore considered out of proportion to attempt virus isolation or tests for virus antibodies

The cause of the increased incidence of elevated ESR in diabetes mellitus has been discussed previously [5 30 34 54]. The differences in frequency of slightly elevated ESR between the two samplings in the present study speak against a connection between ESR elevation and the diabetic state per se at least in the age

groups studied. Due to the exclusion of cases of definite infection and the long interval between the blood samplings it was, however impossible to observe any major differences between cases with normal or slightly elevated ESR as regards titers or bacteriological findings.

It was not possible to demonstrate that the degree of diabetic control in this material had any influence on the ability to form antibodies. It is, however very difficult to evaluate the degree of control over a long period [30] and it is thus not known to what extent the patients might have been ketotic even if the majority on routine out-patient visit, were found to be non-acidotic. Werk & Knowles [63] have recently demonstrated that many clinic ally well adjusted patients nevertheless have an increased amount of circulating ketone bodies. Since the findings of decreased resistance to infection in diabetes have been made on animals [9] and patients [44] in ketosis it seems to be of the utmost importance to make all efforts to avoid this situation. This is further underlined by the findings of a normal response to immunization [61] and restitu tion of the early granulocyte phase of the local cellular response [44] when the patients have been treated and are non ketotic

The formation of antibodies must be considered as only one of the many factors determining the ability of a person to resist infection. A great number of factors have been discussed in connection with natural resistance" to infection, for example environmental factors [1 39 46 and others] nutrition (especially protein [11], vitamins [1] nd iron [?0]) hormones [4 33], phagocytic properties of the reticuloendothelial system [19] and genotypes of both host and parasite [16]. Some of these variables have been investigated in diabetes mellitus. Richard son [49] suggested on the basis of animal studies that the state of cellular nutrition (in his work the amount of liver glycogen) is a significant factor in determining the antibody response. Non-specific defence mechanisms such as the properdin system [12 22, 41], the amount of complement [47] and various activities of whole blood [37] have been found to be essentially normal in controlled diabetes. In alloxan diabetic rabbits *Juhlin [28] found* a decreased phagocytic activity of the reticuloendothelial cells. This may well contribute to a decreased resistance to infection in diabetics, especially in uncon trolled diabetes where hyperlipæmia may cause a "blockage" of the reticuloendothelial syst m [28 35]. The early theory of Lassar [31] that the increased glucose content of the blood and tissues was the responsible factor has been repeatedly questioned [1., 37] and later experimental data [37 48 64] and clinical observations [64] do not favour this view The rela tionship between certain gamma-globulins and immunity is evident [7 1?]. In materials including diabetics with hypoproteinæmia a correlation has been found between antibody response and the serum proteins [14 64] However the level of gamma-globulins as reflected quantitati vely by paper electrophoresis has been found to be essentially normal in the pre sent diabetic group [34]. Nor have obvious signs of nutritional deficiency been b-served [51]

Infectious diseases especially pulmo-

nary tuberculosis, no longer dominate mortality in diabetes mellitus [24 36] An increased morbidity *in tuberculosis, however* still occurs among diabetics [50] but they have no less a chance of surviving than non-diabetic tuberculous patients [24]. There are few modern investigations on the susceptibility of diabetics to other infectious diseases. The increased number of skin and urinary infections in the diabetics of this material cannot be discussed as no systematic registration of these diseases was made Differences in acute common respiratory diseases have been observed in the present investigation but they are more likely to be due to other factors. However the information obtained in this study is not sufficiently evident to exclude the possibility that the diabetic patient may have less ability to overcome illness.

"Resistance to infection is a function of many variables, some of which are definitely recognizable and capable of measurement, while others, probably of equal importance have so far evaded scientific treatment" (cit from Pillemer [45]) In recovery from infectious disease especi ally a disease caused by virus, antibodies probably play only a small part [62] and *studies on such factors as interferons [23 46] may contribute to the confused picture* of infection and diabetes.

Summary

In a group of 145 diabetic schoolchildren, 7–20 years old, and 146 matched non-diabetic controls certain factors relevant to immunity and diabetes were investigated.

The diabetics of all ages were found to have a higher school absenteeism and also, in the prepuberal ages, a higher incidence of acute infectious disease than corresponding non-diabetics. No major dif ferences in the distribution of common bacterial antibody titers were observed and the formation of agglutinins to ty hoid/paratyphoid vaccine was found to be the same in both groups. The diabetics were carriers of common bacteria somewhat more often than the non-diabetics. Most results could not be correlated with the degree of diabetic control.

It is suggested that the explanation of the differences between the two groups might be a longer voluntary phase of recuperation after acute infectious disease in the diabetics.

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Anamnesis, Sweat Electrolyte and Pulmonary Function Studies in Parents of Patients with Cystic Fibrosis of the Pancreas[1]

by M. M. ORZALESI, D KOHNER C. D COOK and H SHWACHMAN

A high prevalence of diabetes mellitus, ulcer cholelithiasis, allergy and chronic pulmonary disease in families of children with cystic fibrosis of the pancreas has been reported by previous authors [6 1., 10] These data if correct, can be interpreted as indicating that cystic fibrosis is due to a single gene made manifest by other genes or environmental factors. In this case the parents and relatives might have minor manifestations of the major gene when it is present alone Alternatively the data have raised the possibility of a detectable heterozygote state On the other hand, reports of other authors [2] are in contrast with these findings. The variability of the results and, in some cases, the inadequacy of the controls led to the present search for a consistent characteristic which might distinguish the heterozygote carrier of cystic fibrosis from the non-carrier With this aim personal and family histories, sweat electrolyte concentrations and pulmonary function were assessed in the parents of children with cystic fibrosis and in a control group.

Material and Methods

One hundred and two parents[2] of children with cystic fibrosis were studied. Except that each parent had at least one child being regularly followed for cystic fibrosis, there was no attempt at selection. There were 39 pairs of parents comprising 76% of the total number The diagnosis of cystic fibrosis in the children was established clinically and confirmed by laboratory examination which included a quantitative sweat test in each patient and duodenal enzyme assay in some of them. In all cases the sweat chloride was more than 90 mEq/l; in six, meconium ileus had been present at birth. The classical signs of chronic pulmonary disease were present and confirmed by X ray in each case. The disease was frequently associated with nutritional and growth disorders; in 16 families more than one sibling was affected with the disease.

The control group consisted of 52 parents of children without cystic fibrosis, but frequently with chronic or serious illnesses (e.g. leukemia or the nephrotic syndrome) These parents were chosen as controls because it was thought that they like the C.F parents, would have been frequently questioned concerning their personal and family histories. The number of pairs of parents in the control group was 20 (77% of the total number).

The groups of C F and control parents were comparable as to sex, age height and

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[2] To be called C.F parents throughout this report

TABLE 1 *Mean height weight age distribution of ages and percentage of heavy smokers in 102 parents of children with cystic fibrosis and 52 control parents.*

		Males		Females	
		C.F parents	Control parents	C.F parents	Control parents
Number		51	26	51	26
Height (cm)		175.8	178.1	160.6	162.9
Weight (kg)		77.2	78.9	59.9	62.6
Age (yrs)		35.2	35.6	34.6	34.2
Per cent distribution (yrs)	20–25	4 %	0 %	6 %	4 %
	25–30	16 %	15 %	20 %	19 %
	30–35	29 %	35 %	25 %	34 %
	35–40	33 %	31 %	31 %	31 %
	40–53	18 %	19 %	18 %	12 %
Per cent heavy smokers*		47 %	50 %	31 %	38 %

* 20 or more cigarettes per day

smoking habits (Table 1) The number of relatives[1] per parent was 5.2 in the C.F group and 4.7 in the control group.

C.F parents and controls were asked identical questions from a questionnaire All parents were meticulously questioned concerning the presence of diabetes mellitus, gastrointestinal disorders (i.e. ulcer cholelithiasis and chronic diarrhea) allergies and chronic pulmonary symptoms (i.e. cough or other respiratory difficulty) in themselves, their siblings and their parents. The disease was considered present only if there was convincing evidence by history Thus, the diagnosis of ulcer and cholelithiasis had to be confirmed by X ray or surgery In the case of diarrhea allergy and chronic pulmonary disease it was not possible to establish such rigid criteria. However again only specif rather than vague signs and symptoms were accepted. In addition each parent had a physical examination of the chest. The anamnesis and examination were carried out by the same person throughout the study

The sweat electrolyte values were measured with local (forearm) iontophoresis using a 64 mg % solution of pilocarpine at 3–4 mA current for 6 minutes [19]. The tests were all performed by the same experienced technician within the five month period from January through May 1962. Eight tests were repeated during this time at intervals ranging from 1 day to 5 months. There was no significant difference in the values obtained. The mean difference between two determinations on the same subject was 4.4 ± 1 6 mEq/l for sodium, 2.4 ± 1.6 mEq/l for chloride and 1 25 ± 1 15 mEq/l for potassium.

The pulmonary function tests included measurement of vital capacity and timed vital capacity (2 seconds) using the apparatus described by Gaensler [10], measurement of peak expiratory flow rate using the instrument described by Wright [23] and maximal breathing capacity Twenty-three of the C F parents and 11 of the control parent also had studies of their intrapulmonary distribution of gas as estimated from their nitrogen washout curves [5 9].

The vital capacity measurement was chosen because of its simplicity and reproducibility Airway obstruction is an important and almost constant feature of cystic fibrosis [7 17] and, therefore tests of timed vital capacity maximal breathing capacity and peak flow rat were used. The more exact measurement of airway resistance was

[1] Relatives of the C F and control parents in this study include only their parents and their siblings.

TABLE ... *Personal history of parents of children with cystic fibrosis and control parents*

		Chronic cough		Allergy		G I tract*		Diabetes	
	No.	No.		No.	%	N	%	No.	%
C.F parent	102	1	11.8	30	28...	7	6.9	1	1
Control parents	82	6	11.5	13	...5.0	4	7	0	0

When ulcer and cholelithiasis are considered separately their prevalence is not significantly different in the two groups.

not used because of its complexity and hence limited applicability to large numbers of patients. However because varying degrees of airway resistance in the air passages tend t produce irregular gas distribution, in some of the C.F parents and in some control parents unevenness of ventilation was calculated from nitrogen washout curves by the method proposed by Briscoe & Cournand [6].

For the nalysis of the measurement of vital capacity maximal breathing capacity and peak expiratory flow rate the two groups of subject were subdivided according to sex and height The sex of the individual ppeared to influence the nitrogen washout and was, therefore taken into account in the analysis of this test. The timed vital capacity is apparently not influenced by height

Results

The pertinent data from the personal and family histories are shown in Tables * and 3 Using the X^2 test no significant differences could be found in the prevalence of any of the conditions investigated when the C.F parents were compared with the control group Similarly no significant differences were found between the two groups when the data were extended to include the siblings of the parents and their parents. These findings are in agreement with those reported recently by Anderson and co-workers [ ]. Among the parents themselves it was noted that the heavy smokers in both groups more frequently had a chronic cough (22.6 % of the heavy smokers) than the persons who smoked less or not at all (4.3 %), ($P<0.005$)

The chest examination was negative in all individuals of both groups

Th regression lines xpressing the correlation between the sodium and chloride concentrations in the sweat were

TABLE 3. *Family history of pare ts of ch ldren with ystic f brosis and f control parents*

	No. of individuals	Allergy		G.I tract		Diabetes	
	Total N	N		No.		No.	%
C.F parents and families	629	—	1...2	41	6.5	10	1.6
Control parent and families	294	...3	8.5	22	7.5	7	...4

This includes the parents themselves, their siblings and their parents. The category of chronic cough was omitted from his t ble because of the vagueness of such history in ll but the parents themsel es

When ulcer and holelithiasis are considered separately their prevalence is not significantly different in the two groups.

TABLE 4 Sweat test results in 102 parents of children with cystic fibrosis and 52 control parents

	No.	Sodium (mEq/l) Average ± S.D	Chlorid (mEq/l) Average ± S.D	Potassium (mEq/l) Average ± S.D	Sweat weight (mg) Average ± S.D
C.F parents					
Males	51	45.0 ± 14.8	34.3 ± 12.9	7.22 ± 1.3[a]	331.3 ± 119.5[b]
Females	51	44.4 ± 15.5	31.8 ± 12.8	8.43 ± 2._	228.0 ± 113.2
Control parents					
Males	26	43.4 ± 19 7	30.4 ± 16.8	7.86 ± 2.0[a]	333.0 ± 115.5[b]
Females	26	42.8 ± 18.5	26.9 ± 16.9	8 74 ± 1.9	226.3 ± 91.9

Significant difference between males and females. $P < 0.05$ for C.F parents, $P < 0.025$ for controls.

[b] *Significant difference between males and females, $P < 0.001$ both for C.F parents and controls.*

similar in the C.F and control parents ($F = 1\ 405$) so that it was possible to consider them as one group in the calculation of the correlation coefficient (Fig 1) The relation between sodium and chloride concentrations was close ($r = 0\ 934$) and was represented by the following equation.

$$Cl = 0\ 806 \times Na - 4\ 04$$

The means of the sodium chloride and potassium concentrations in the sweat and the mean sweat weight of the C.F and control parents are shown in Table 4 No significant differences between the two groups were found. The distribution of the sodium and chloride levels was also similar (Fig 2) The sodium and chloride concentrations showed a tendency to increase with age only among the controls (Table 5); nevertheless, even when age was taken into consideration there was still no significant difference in the values of the sweat electrolytes between the C.F and control parents.

The results of the pulmonary function tests are shown in Table 6 With three exceptions which are probably related to the relatively small number of controls in these particular subgroups there were no significant differences between the C.F and control parents.

When the results were further analyzed,

TABLE 5 Sweat electrolyte values according to age in 102 parents of children with cystic fibrosis and 52 control parents

Age group (yrs)	C F parent			Control parents		
	No. of individuals	Sodium (mEq/l)	Chloride (mEq/l)	No. of individuals	Sodium (mEq/l)	Chloride (mEq/l)
20–30	23	43 0	33.6	10	35.4	22.0
30–35	28	44.7	33.0	18	40.6	27.6
35–40	33	46.5	35.5	16	45.4	29.9
40–45	18	43.7	30.5	8	53.6	37 0

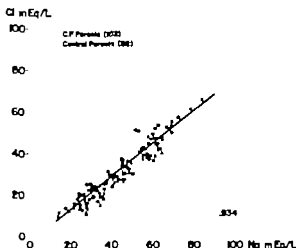


Fig. 1. Correlation between sodium and chloride concentrations in the sweat of 102 parents of children with cystic fibrosis (●) and 5_ controls ( ). The regression line calculated from the actual values is shown.

no correlations between the personal and family history sweat test and pulmonary function tests could be found in either group of parents. In particular the sweat electrolyte values were not elevated in the parents (both C.F and controls) with personal history of ulcer or allergy. This was in contrast with the findings of other authors [11 1]. Similarly when the effect of sex and age was taken into consideration, no significant association was found between low pulmonary function tests and elevated sweat electrolytes in either group of parents.

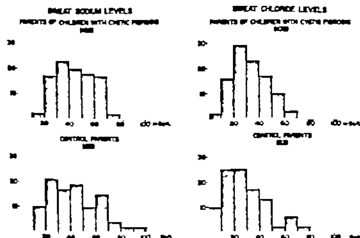


Fig. 2. Distribution of sodium and chloride levels in the sweat of 102 parent of children with cystic fibrosis and 5_ controls.

TABLE 6 *Results of pulmonary function tests performed on the parents of children with cystic fibrosis and control parents.*

Sex	Groups according to height	Number		Mean height (cm)		Vital capacity (l) Average ± S.D.		Maximal breathing capacity (l/min) Average ± S.D.		Peak flow rate (l/min) Average ± S.D.		Timed vital capacity (3 sec)		Nitrogen washout (% delay) Average ± S.D.	
		C.F parent	Control parent	C.F parent	Control parent	C.F parent	Control parents	C.F parent	Control parent	C.F parent	Control parent	C.F parent	Control parent	C.F parent	Control parents
Males	Ht < 175 cm	21	12	169.6	170.7	4.60 ±0.40	4.77 ±0.47	151 ±18	138 ±14	619 ±87	616 ±42	80 %	90 %	28 % ±17.4	9 % ±10.6
	Ht > 175 cm	30	14	180.3	180.8	5.11 ±0.84	5.20 ±0.45	157 ±31	146 ±34	543 ±80	555 ±55				
Females	Ht < 160 cm	23	5	155	157.3	3.30 ±0.43	3.28 ±0.16	96 ±17	94 ±16	377 ±67	429* ±31	91 %	9* %	30 % ±12.8	33 % ±21.5
	Ht > 160 cm	28	21	164.1	164.5	2.69 ±0.58	3.72 ±0.33	101 ± 17	96 ±16	399 ±34	397 ±58				

Significant difference P 0.025 for maximum breathing capacity $P < 0.01$ for peak flow rate $P < 0.05$ for nitrogen washout.
This test was performed only in 60 C.F parent equally divided among males and females.
The nitrogen washout was performed on 23 C.F parents (11 males and 12 females) and on 11 control parent (5 males and 6 females).

Discussion

Much of the controversy concerning the incidence of cystic fibrosis, its genetic pattern and the presence or absence of associated diseases results from the variability of the definition of the disease itself. In recent years the measurement of sweat electrolyte concentrations has greatly facilitated the diagnosis of cystic fibrosis in children. Since over 15 % of patients with cystic fibrosis have considerable pancreatic function and because of the relative difficulty in analyzing duodenal contents for pancreatic enzymes and viscosity and the relative simplicity of the sweat test, more and more reliance has been placed on the latter [18]. As a consequence, although a number of authors have established the variability of sweat electrolyte concentrations and the multiplicity of factors affecting them, sodium and chloride concentrations in excess of so-called "normal" values have been frequently but incorrectly assumed to establish definitely the diagnosis of cystic fibrosis of the pancreas. There seems no doubt from the work of Lobeck & Huebner [14], who found 17 % of their adult control subjects to have sodium concentrations of more than 70 mEq/l and from the present data showing 15 % of the control subjects sodium concentrations over 70 mEq/l, that the diagnosis cannot be established on the basis of sweat electrolyte concentrations alone.

In the present study as rigid criteria as possible were used to establish the diagnosis of cystic fibrosis in the propositi and no doubtful or borderline cases were included. When the prevalence of a number of conditions in the parents, grandparents, uncles and aunts of these children were compared with the prevalence in control families, no significant differences could be found. There was somewhat more allergy in the C.F. parents than in the control group but this was not significant ($P = <0._$). The difference between the prevalence of allergy in the parents themselves and in their families (cf. Table * vs. Table 3) is probably related to the fact that they knew their own allergic manifestations better than those of their relatives. In any case, the occurrence of allergy in both the C.F. families and the controls is somewhat higher than usually accepted for the population as a whole. This may be because the diagnosis was based on history alone rather than history plus specific tests for sensitivity or because of random variations in the selection of the test population. With more definite entities such as gastrointestinal ulcers, gall stones or diabetes, there was no significant difference between their occurrence in the parents themselves and the occurrence in the family constellation. The prevalence of known diabetes in both C.F. families and in controls was within the limits reported for the general population [1].

A number of authors [8, 13, *0] have reported significantly elevated concentrations of sodium and chloride in the sweat of relatives of patients with cystic fibrosis, while others [1, 14, 15] have found no difference between the relatives and control subjects. The present data seem to confirm the latter finding; i.e. the C.F. parents have sweat sodium and chloride levels which are not significantly different from those of the controls. However, as Karlish and co-workers [13] have pointed out, the discrepancy in the results of the sweat tests in the C.F. parent may be due to the

method used. In fact, only authors [8, 13, 20] using thermal stimulation found higher values in the parents and siblings of patients with cystic fibrosis.

The sweat weight was significantly higher in the males than in the females in both C.F. and control parents ($P = <0.001$) a finding which confirmed the results of Lobeck & Huebner [14]. The males also tended to have a sweat level of sodium and chloride higher than the females, this finding may be related to the different rate of sweating in the two sexes. Furthermore, in both groups the potassium level was significantly lower in males when compared with the females. In addition, in the controls, the sodium and chloride levels increased with age.

No pulmonary function tests have been reported for a group of parents selected only because they had children with cystic fibrosis. The present data, which particularly pertain to the evaluation of airway resistance, indicate no airway abnormality in the C.F. parents when compared with the control group. The fact that in one group the maximal breathing capacity of the C.F. parents was "significantly" better than the controls and in another group the peak expiratory flow rate was significantly higher in the control group is probably related to the small number of individuals involved. Indeed when the subgroups are combined the apparent differences disappear.

There appears to be a significant difference in the results of the nitrogen washout for one group of parents, but the average value of 0 % washout delay for the control fathers is based on only five determinations. If the value of 16 % ± 9 % washout delay reported by Briscoe & Cournand [6] for normal adult males is used, then the group of C.F. fathers must be considered normal. The C.F. mothers appear to have no significant delay in nitrogen washout when compared with the controls.

The present study is the first to attempt to quantitate both sweat electrolytes and pulmonary function tests in parents of patients with cystic fibrosis and control parents, and to correlate the two types of tests. No significant association was found between pulmonary function tests more than 1 S.D. below the average and sweat electrolyte levels more than 1 S.D. above the average in either C.F. or control parents. Since our parents have pulmonary function tests within the normal limits, this finding is not inconsistent with the results of other authors who have reported high sweat electrolytes in patients with severe emphysema [3, 16, 22] and bronchiectasis [13].

In conclusion, the results of this study provide no evidence that cystic fibrosis is inherited as a dominant disease as suggested by Bohn & Koch [4]. In addition, attempts to differentiate heterozygote carriers of the disease by history, sweat electrolyte concentrations and pulmonary function tests were unsuccessful.

Summary

One hundred and two parents of children with cystic fibrosis and 52 control parents were studied with regard to physical examination of the chest, personal and family history, sweat electrolytes and pulmonary function tests.

The physical examination of the chest was negative in all parents.

When the C.F. parents were compared

with the control group, no significant differences could be found in the personal and family histories of chronic cough allergy gastrointestinal disorders (ulcer and cholelithiasis) and diabetes.

The concentration of sodium, chloride and potassium in the sweat (produced by iontophoresis) was similar in the two groups of parents.

The pulmonary function tests (vital capacity timed vital capacity peak expiratory flow rate maximal breathing capacity and nitrogen washout) showed no significant differences between the two groups of parents.

This study provides no evidence that cystic fibrosis is inherited as a dominant disease

By the methods used no particular characteristics were found which could differentiate the heterozygote carrier of cystic fibrosis from the non-carrier

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Quantitative Bacteriological Examination of Urine in Children with Urinary Tract Infections

by ARVE LYSTAD and ODD GARDBORG

Urinary tract infections are among the most frequent and important types of infectious diseases. In recent years these infections have been regarded with increased attention.

A large number of post mortem examinations [17 23] has made it apparent that pyelonephritis is the most frequent kidney disease, and that a considerable proportion of the cases are never diagnosed *intra vitam* In a number of adult patients chronic pyelonephritis dates back to childhood.

With children, urinary tract infections generally make their appearance early in most cases before the age of two Frequently such an infection is never cured, becoming a latent pyelonephritis which may occasionally flare up or develop into steadily advancing disease leading to renal failure, uremia and death [1 12 17 22, 27] It should briefly be mentioned that pyurias of childhood are very often related to congenital anomalies in the urinary tract and urological examinations and surgical treatment of obstructions are of prime importance

On the basis of the above-mentioned, it will be readily seen that infections of the urinary tract in children must not be neglected. The diagnosis should be established as soon as possible adequate therapy must be applied and the patient regularly and thoroughly checked In spite of the many effective chemotherapeutic agents and antibiotics at our disposal today results are far from satisfactory as a number of the patients either do not get rid of their infections or are subject to relapses.

Material

From the beginning of April t the end of December 1961 287 urine specimens were examined from patients at Children Hospital, University f Oslo (Table 1).

Clean voided specimens were consistently taken from the boys, while partly clean oided, partly catheterized specimens were examined from the girls. Since very few children under the age of three will pass urine when asked to, these patients were arranged in a separate age group. In this group the clean voided specimens were taken in a slightly different way (cf below)

The examination of clean voided and catheterized specimens were compared in 50 double specimens from 49 girls without infection (the norm) and in 35 double specimens from 33 girls with urinary tract infection

TABLE 1 *Age and sex distribution.*

	0–3 years		3–12 years		
	Girls	Boys	Girls	Boys	Total
A: Patients with urinary tract infection					
1 Known obstruction and/or other anomalies	8	12	37	13	70
2. Free of obstruction and/or other anomalies	9	9	20	10	48
Total	17	21	57	23	118
B Patients without urinary tract infection (the norm)	21	0	28	0	49
Total	38	21	85	23	167

Methods

The specimens from girls over the age of 3 years, were obtained as follows:

1 The perineum and vulva were washed for a few minutes with warm soap water then rinsed with clean water

2. Afterwards they were washed with sterile swabs moistened with 1 % benzalkonium chloride. Each swab was only used once washing from the front towards the back. This process was repeated three or four times.

3.*a*. A sterile catheter lubricated with sterile oil or gel was introduced into the bladder and about 10 ml of a midstream specimen was collected in a sterile test tube which was closed with a sterile cotton plug

3.*b* To obtain a clean voided sample a midstream specimen was collected in a sterile urine glass, about 10 ml of this was transferred to a sterile test tube, which was then closed.

The collecting of specimens from boys was as follows:

1 The prepuce was drawn back and the glans and prepuce carefully washed with lukewarm soap water followed by a thorough rinse with clean water

2 Then the glans was washed with swabs moistened with 1 % benzalkonium chloride

3. The boys then passed urine the first 5 ml being discarded and the next 10 ml collected in a sterile test tube which was immediately closed with a sterile cotton plug

To obtain clean voided specimens from girls and boys under the age of 3 years, the children were washed as described above and a sterile plastic bag was attached The child was kept under constant observation so that the urine in the bag never remained with the child for more than half an hour

All specimens are of morning bladder urine. The test tubes were immediately sent to the bacteriological laboratory and examined within an hour or two If the specimens could not be examined at once, they were refrigerated [19 20] Hoeprich quantitative method [10] was followed. A slide for microscopic examination stained by the Gram method, (uncentrifuged urine) was also prepared. The criterion for a positive Gram preparation was that bacteria could be found in any microscopic field. (At least 20 fields were examined.)

After spreading the urine on blood agar and bromthymolblue lactose agar plates, the cultures were incubated overnight at 37°C [20]. The isolated microbes were identified by the usual biochemical methods, and if there were more than 100,000 bacteria per ml of urine, sensitivity tests were performed.

Sensitivity towards antibiotics and chemotherapeutics was tested by a disk method described by Ericsson, Högman & Wickman [4]

The presence of more than 100,000 bacteria per ml of urine was taken as a sign of infection, fewer than 10 000 bacteria

TABLE _. *Distribution of the various bacterial species among the three groups: A definite infection B uncertain result C no infection*

Species	Group A $> 10^5$	Group B $< 10^5$ $> 10^4$	Group C $< 10^4$
	No. of microbes per ml of urine		
E. coli	51	13	1
Proteus	16	8	2
Aerobacter	15	0	
Enterococcus	14	9	1
Mixed culture	6	8	13
Paracolobactrum	6	0	0
Micrococcus, Streptococcus viridans, Staphylococcus albus, Lactobacillus	3	5	9
Pseudomonas	0	2	0
Staphylococcus aureus	3	1	0
Candida albicans	2	0	0
Total	116	41	48
No growth			82
Total	116	41	130

per ml were regarded as indicative of no infection or of contamination. Results between these two limits were designated in conclusive and new test recommended [12, 14, 15, 16].

In all cases of urinary tract infection the results of the bacteriological examination were compared with the clinical symptoms and the dat of taking of the sample and the commencement of therapy noted, the nature and duration of therapy and any development of drug resistance by the microbes responsible.

In the case of the 83 patients where clean voided nd catheterized specimens were compared, these were taken t 24-hour intervals.

Result

Out of a total of 287 tests taken from 118 patients, 116 tests contained more than 100 000 bacteria per ml urine 41 contained between 10 000 and 100 000, and 130 contained fewer than 10 000 bacteria per ml or showed no growth Table 2 shows the distribution of various types of bacteria found in the three groups. Group A. Definite infection (more than 100 000 per ml urine) Group B Uncertain result (between 10 000 and 100 000 per ml urine) and Group C No infection (fewer than 10 000 per ml urine)

Table 3 shows the percentage distribution of those microbes which were found in significant number (Group A) The E. coli and Aerobacter groups alone constitute about 62 % of the total. Th group other bacteria is made up of Pseudomonas eruginosa, Staphylococcus aureus, Micrococcus, Staphylococcus albus Streptococcus viridans and Lactobacillus.

Gram-stained smears of uncentrifuged urine have been examined in 283 samples (Table 4) In Group A 106 were positive eight uncertain and two negative in

TABLE 3 *Distribution of microbes found in significant numbers in urinary tract infections among children.*

Species	No. of specimens	% distribution
Escherichia coli	51	44
Proteus types	16	14
Aerobacter	15	13
Enterococcus	14	11
Paracolobactrum	6	5
Mixed culture	6	5
Other bacteria	8	8
Total	116	100

TABLE 4 *Comparison between direct microscopy of gram-stained preparation of uncentrifuged urine and cultivation results.*

Direct microscopy of gram preparation	A $>10^5$	B $<10^5$ $>10^4$	C $<10^4$	Total
Microbes present	106	1	0	107
Uncertain result	8	12	0	20
Microbes not evidenced	2	26	128	156
Total	116	39	128	283

Group B one positive 12 uncertain and 26 negative; and in Group C all were negative

Table 5 shows the relation between the clinical and the bacteriological findings. Patients who because of their symptoms and the microscopic evidence of pyuria have been clinically interpreted as suffering from urinary tract infections are listed in Group I. In the case of patients not treated for infection, all 44 specimens come under Group A (more than 100 000 bacteria per ml urine) In patients who received treatment for infection, we have distinguished between specimens taken from patients who at the time showed no clinical response to therapy (persistent pyuria) and specimens taken from patients who had responded favourably to therapy Of specimens taken from the former 66 fell under bacteriological Group A, 32 under Group B and none under Group C Of those taken from patients showing clinical response to therapy none fell under Group A five under B and 94 under C There are specimens from a total of 85 patients with clinical infection.

Specimens obtained from the 33 patients who were free of infection at the time are divided as follows. six in bacteriological Group A, four in Group B and 38 in Group C

There are altogether 110 specimens from 54 patients (Group I*a*, and *b* in Table 5) with clinical infection, and these reveal bacteria in excess of 100 000 per ml of urine Forty-six specimens from Group I*b* come from patients whose microbes have become resistant [4] to an antibiotic or a chemotherapeutic agent during the course of treatment. Six of these patients have been given all the usual antibiotics and chemotherapeutic agents in turn with development of drug resistance to each one The last 20 specimens in clinical Group I*b* come from patients who have been given inadequate treatment or whose infection has flared up again after the treatment was suspended. In these cases there was no demonstrable development of drug resistance

Fig 1 shows the relation between clean voided and catheterized specimens obtained from girls with untreated urinary tract infection 17 double specimens from 16 girls, and the same relation with samples taken from girls free of urinary

TABLE 5 *Distribution of analysed specimens in relation to the cl nical findings*

Clinical findings	Microbes per ml of urine A $> 10^5$	B $< 10^5$ $> 10^4$	C $< 10^4$	No. of patients
I. Infection				
( ) Specimens from untreated patients	44	0	0	
(b) Specimens from patient treated (without clinical effect)	66	32	0	85
(c) Specimens from patients treated (with clinical effect)	0	5	94	
II Specimens from patients free of infection t the time	6	4	36	33
Total	116	41	130	118

tract infection, a total of 50 double specimens from 49 patients. In addition, we analysed a further 18 double specimens from 17 girls with urinary tract infection These patients were however undergoing treatment with antibiotics and/or chemotherapeutic agents at the time when the specimens were taken, so that these results showed considerable bacteriological variation from sample to sample and are thus unsuitable as a basis for comparison of the two techniques of sample taking These later figures are consequently not included in Fig 1

Discussion

Diagnosis One of the most important features of the diagnosis and the most correct basis for treatment of urinary tract infection is reliable bacteriological examination coupled with sensitivity tests. This is, however not so easily achieved with those techniques which have hitherto been employed in bacteriological urinary examinations, the chances of contamination during the taking of th samples always being great. Contamination derives from the urethra itself and its immediate surroundings, often consisting of the same types of bacteria that cause urinary tract infections [6, 7 *1 4 28 34]. It is often possible to isolate microbes in small quantity in the urine of both children [*1] and adults [28] who show no sign of urinary tract infection. It is obvious that the mistake of performing sensitivity tests on microbes, causing contamination and directing therapy against those could easily occur Herein probably lies the explanation why bacteriological examinations of urine have been in disrepute in many clinics.

In addition to the bacteriological findings, there is in most cases also the clinical evidence as a basis for diagnosis Yet research has shown that bacteriuria may

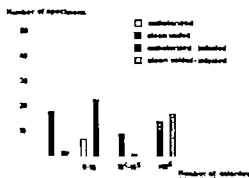


Fig 1 Paired clean voided and catheterised specimens taken from girls with untreated urinary tract infections (17 pairs from 16 girls) and from girls free of urinary tract infection (50 pairs from 49 girls).

be the only symptom in cases of pyelonephritis [11 13 15 17] This emphasizes anew the significance of bacteriological urinary examinations.

The *quantitative bacteriological* examination in suspected infections of the urinary tract essays to create a logical basis for diagnosis and therapy

As early as *1922 Helmholz & Millicken* [8] demonstrated that the possibility of contamination while the specimens were being taken was great and that bacteria *occurring in urine specimens did not* necessarily originate in the urinary tract. In 1940 Marple commenced quantitative bacteriological examination of urinary *tract infection in women [25] Kass in* a number of papers [14 15 16 17] has attached considerable importance to quantitative bacteriological urine examinations, and credited these with great significance He has stipulated a bacteria count of 100 000 per ml of fresh sample of morning bladder urine as a criterion of infection, a bacteria count between 10 000 and 100 000 per ml of urine as inconclusive but with the recommendation that a new test be made and a bacteria count of less than 10 000 per ml of urine as infection free with probable contamination. These same delimitations have been accepted by others [10 12 13] in similar work. Pryles [*9], however says that as far as children are concerned urines containing less than 1000 colonies/ml are indicative of contamination, urines containing between 1000 and 100 000 colonies/ml are to be suspected of infection and studies repeated, and urines containing more than 100 000 colonies/ml are indicative of infection Judging by our investigations, this limit of 1000 colonies per ml seems to be set too low as most contaminations give up to 10 000 bacteria per ml of urine.

Bacterial flora. Our investigations reveal that bacteria from the coli-aerobacter group proteus types and enterococci dominate this group of infections (Group A) These bacteria are found to be the chief cause of urinary tract infections [5]. The same bacteria however also dominate in Group C In addition large quantities of saprophyte microbes are found in this group The mixed culture consists largely of pathogenic microbes in Group A, but are mixed with saprophytes in Groups B and C The majority of our samples come *under Groups A and C, a minority in the* uncertain Group B This agrees well with similar investigations [16]

It has previously been indicated [6 7 *1 24 28 34] that representatives of the most important microbes which cause urinary tract infection (such as E. coli, proteus and enterococci) are to be found in the urethra under normal circumstances. Occurrence of these bacteria in urine specimens do not necessarily indicate urinary tract infection, the amount of bacteria must also be taken into consideration.

Microscopy The agreement between the results of the bacteriological examination and the direct microscopic examination of a gram-stained preparation of uncentrifuged urine support the use of direct microscopy in diagnosing urinary tract infections. To doctors who do not have the opportunity of cultivating microbes, this method can be of great help The normal microscopy of urine sediment is not of course rendered superfluous but these two methods can *surely supplement* one

another in a way that can render the doctor great assistance [9]

Pyuria. There is lacking however a good definition of the concept pyuria, and consequently there is considerable disagreement as to the number of leucocytes found in normal urine samples. Wilson & Schloss [36] used the term to designate "the presence of sufficient pus to cause definite cloudiness of urine Cambell (cited by Pryles [29]) considers three to five cells per low power field in an uncentrifuged catheter specimen to be within normal limits. Helmholz (cited by Cambell) has stated that two to eight cells per low power field are normal Stevenson [35] considers up to two to four leucocytes per low power field from an uncentrifuged specimen, as normal. Pryles & Lüders [30] and Anderson (cited by Pryles [29]) have defined pyuria as the presence of five or more leucocytes per high-power field in a centrifuged specimen of urine

We have defined pyuria as the presence of more than six to eight leucocytes per high-power field in a centrifuged specimen of urine. The amount of urine and the speed and duration of centrifuging have been kept constant as far as possible (about 600 g in 3 min)

Most authors are in agreement that extrarenal causes of pyuria must be excluded before a pyuria is interpreted as a urinary tract infection

Bacteriological and clinical findings The correlation between bacteriological and clinical findings obtained in this investigation is very good (Table 5) Altogether there are only five specimens out of 143 where there is no correlation between clinical sign and the bacteriological findings. The five in question belong to the group with a bacteria count between 10 000 and 100 000 per ml of urine We have a further 98 specimens from patients with clinical infection, divided into 66 with over 100 000 bacteria per ml of urine and 32 in the uncertain group Investigation of the records reveals that these were taken from patients who were undergoing treatment at the time when the samples were taken. This may explain the relatively large proportion (about 30 %) falling in the uncertain group This shows that if the diagnosis is to be based upon quantitative criteria the specimens must be obtained under special conditions which *i ter alia* specify that the patient must not be receiving treatment

It must be stressed that there should be a comparatively long interval between suspension of preceding medicinal therapy and commencement of the bacteriological examination before quantitative criteria are accorded decisive importance The apparent discrepancies between clinical findings and quantitative analyses found in certain instances can in the vast majority of cases be accounted for by the fact that the patients had recently received anti bacteria therapy In some instances the discrepancy cannot be explained, and there is reason for underlining that the method can occasionally fail even when the best technique is employed The results must be judged critically as in most clinical tests of a similar nature [9] In doubtful cases further tests will as a rule resolve any ambiguity

In 33 of the patient urinary tract infections were repeatedly found, but at the time when the specimens were taken there was no clinical infection Out of 46

samples, 36 come under Group O (Table 5) Six of the remaining 10 specimens are direct mistakes with bacteria count of over 100 000 per ml of urine, without there being any sign of clinical infection at the time. These mistakes show that our technique is not 100 % quantitative, or perhaps these findings express actual bacteriuria in patients without any other indication of urinary tract infection such as certain authors have previously described. This may also apply to the four specimens which come in the uncertain category

The agreement between the bacteriological and the clinical findings shows that the lower limit of 100 000 bacteria per ml from a fresh sample of morning bladder urine as an indication of infection, seems to be correct. There are only the 3? specimens in the bacteriologically uncertain category which might point towards a lower limit of perhaps 10,000 bacteria per ml Against this, however it must be pointed out that these specimens were taken from patients receiving treat- and it is only to be expected that readings show a downward trend

Our investigations confirm the results from previous quantitative bacteriological investigations, and it would seem that the boundary set between infection and contamination can be accepted This provides a far safer basis for medicinal therapy by leading to the discovery of the microbe responsible for the infection and removing the chances of being misled by contaminations. There is reason for hope that this will in time result in improved results of treatment and increased confidence among doctors in the value of bacteriological examinations.

Development of resistance A very important point is the relatively strong tendency for microbes to develop resistance [4] during treatment with chemotherapeutic agents or antibiotics. In as many as 46 out of 110 patients from whom specimens were taken and where there was bacteriological/clinical correspondence resistance had been developed during treatment.

Anomalies and obstructions Anomalies and/or obstructions in the urinary tract are in many cases a natural explanation of the cause of repeated infections [18 ?7] The material on which this study is based shows that 70 out of 118 patients (about 60 %) with urinary tract infections had anomalies and/or obstructions. With several patients many such conditions occur in combination.

Catheterisation versus clean voided specimens Pryles and his assistants [29 31 32] have in recent years accorded quantitative bacteriological examination of urine great significance in diagnosing urinary tract infections in children. They have furthermore carried out several examinations in which the clean voided and catheter specimens were compared. Their investigations show that catheterisation as diagnostic method can and should be confined to special cases and then only when absolutely necessary Clean voided specimens are completely adequate if the patient has been pretreated as with catheterisation. Pryles & Steg [32] find positive correlation between catheter and clean voided tests in 96.5 of the cases, when the samples are taken with a standardized technique The time interval between the two tests was under 1 hour

The problems which Pryles and his

assistants have illuminated have also been taken up in this investigation. The question we posed ourselves was whether clean voided specimens taken *lege artis* can replace catheterization also in the case of girls. When it is realised what kind of flora can be found in the urethra and its surroundings in normal children [°1], it is not difficult to imagine that catheterization can induce urinary tract infection with these microbes. Also catheterization produces a serious psychic trauma in many children. It would therefore be a great gain if another method of taking these tests could replace catheterization without impairment of diagnostic efficiency [26 33]. In common with Beeson and Guze [2 3, 6], Kass has also shown that there is increased frequency of urinary tract infection as a result of catheterization.

By means of the quantitative method it is almost always possible to differentiate between contamination and infection [16 19 26, 33]. Where the bacteriological findings are inconclusive catheterization can, if necessary be resorted to after repeated tests.

The investigations here made for comparing the dependability of clean voided and catheterized specimens deviate somewhat in method from those undertaken by Pryles and his assistants in that our tests were taken at 24 hours intervals. The conditions for establishing the cited limits between infection and contamination, presuppose *inter alia* that the urine has been in the bladder during the night (morning urine)

Our material derived from infected patients together with the 50 double specimens taken from 40 girls free of infection seems suitable for a comparison of the two methods. The normal material (Fig 1) shows correlation in 41 out of 50 double specimens. As criterion of correlation, the presence in both specimens of a microbe reading within the same bacteriological group was required. The nine double specimens which show no correspondence have a bacteria reading of fewer than 10 000 per ml of urine in the case of catheter test, while with the clean voided it varies from 15,000 to 65 000 Clean voided samples thus still reveal a count of less than 100,000 per ml, i.e under the lower limit of infection.

Of the 17 double specimens obtained from 16 patients with untreated infection, there is correlation in 14 Two catheter specimens have a reading fewer than 10 000 per ml, and one shows a count between 10,000 and 100 000 per ml where the clean voided shows reading over 100 000 Twelve double specimens out of 67 reveal no correlation. Altogether there is a correspondence between clean voided and catheter specimens in about 82 % of the cases.

An advantage of the quantitative method is that the number of catheterizations can, also in the case of girls, be appreciably reduced. It is naturally an important condition that clean voided specimens be taken with the greatest care since the risk of massive contamination is here particularly great. In case of doubt t will lways be possible to make repeated tests and to carry out catheterization where bsolutely necessary The fact that this method takes a little time should not weigh too heavily when the risk which catheterization involves is taken into consideration.

The significance of bacteriuria alone has been much disputed, but most now consider it as a fairly reliable index of urinary tract infection. Quantitative bacteriological analyses will in such cases be of particular assistance in determining whether the number of bacteria present in such infections is significant or not.

Summary

Quantitative bacteriological examinations have been carried out in 287 urine specimens from 74 girls and 44 boys with urinary tract infection (17 girls and 21 boys below the age of 3 years and 57 girls and 23 boys between 3 and 12 years of age). Clean voided specimens were consistently taken from the boys. Partly clean voided partly catheterized specimens were taken from the girls. Gram-stained smears from the urine specimens were also examined in the microscope.

The investigations show a good correlation between quantitative bacteriological results and clinical findings. The lower limit of 100 000 bacteria per ml from fresh samples of bladder urine as an indication of infection seems to be correct. There is good agreement between the results of the quantitative bacteriological examinations and direct microscopic examination of gram-stained smears of the uncentrifuged urine. This supports the use of direct microscopy in diagnosis of urinary tract infections.

In 50 double specimens from 49 girls without infection (the norm) and in 33 double specimens from 23 girls with urinary tract infection a correspondence was found between clean voided and catheter specimens in about 83 % of the cases. It may be concluded that clean voided specimens taken lege artis and followed up by quantitative bacteriological examination should yield a reliable diagnostic method. The quantitative method can be used to distinguish between infection and contamination.

The investigations indicate a strong tendency for microbes to develop resistance during treatment with chemotherapeutic agents or antibiotics. This emphasizes the importance of repeated bacteriological examinations of patients with urinary tract infection.

The importance of obstruction as an etiological factor in urinary tract infection in children is supported.

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CASE REPORT

Ectopic Liver in Omphalocele

by GUSTAF FOCK

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The macroscopic structure of the liver is fairly constant, and variations of any noteworthy degree are infrequent.

According to Cullen [2] a liver fragment attached to the main portion of the liver by a thin pedicle is a rare phenomenon. Completely free ectopic liver tissue is of extremely infrequent occurrence and this anomaly has been described only in a mere handful of cases.

Kaufman & Mandoff [6] described an ectopic lobe of the liver located intrathoracically to the right above the diaphragm. Elserth [9] described 13 cases in which ectopic liver tissue had been observed. In all these cases the ectopic liver tissue occurred in the abdominal cavity and in most it was attached to the liver itself by a pedicle.

In the Children's Clinic of the University of Helsinki two newborn patients have been encountered, both of whom displayed an omphalocele containing completely detached ectopic liver tissue.

Case 1

(Case history 4973/-61.) The patient, a girl, was at birth a mature infant weighing 3350 g. She was otherwise normally developed except for a cherry-sized omphalocele on account of which she was admitted to hospital. Three days later the omphalocele was surgically removed. It proved to be empty with the exception of a small omental flap attached to the apex of the anomaly. Postoperative recovery was uneventful.

Pathologist's report (L. Hjelt, M.D.). The specimen is enclosed by a membrane well supplied with blood vessels. The membrane encloses liver tissue, the lobular structure of which is completely irregular. The smaller biliary ducts are empty and atypical. Hematopoiesis occurs in the hepatic tissue. Adjacent to the ectopic liver and separated from it by a thick layer of connective tissue is seen a rudimentary gall bladder.

Case 2

(Case history 6038/-61.) The patient was a newborn girl weighing 3100 g. She was healthy and well developed except for a small omphalocele. At the age of 11 days the patient underwent an operation during which it was ascertained that the omphalocele sac did not contain any abdominal organs but that a urachal duct was attached to it. The urachus was resected and nothing else of a pathological nature was found in the abdominal cavity. The patient made an uneventful recovery.

Pathological examination (L. Hjelt, M.D.). The specimen is covered for the most part with skin of normal appearance. In the centre of the specimen there is a small piece of hepatic tissue in which the lobular structure is distinctly visible. The biliary ducts appear to be normal. Their lumen is

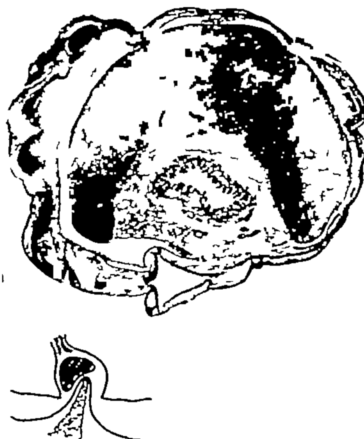


Fig. 1 Case 1 The cavity in the centre is the gall bladder A. The insertion shows conditions t operation.

narrow and no bile pigment is present. The liver tissue is surrounded by concentric layer of connective tissue.

Comments

The most frequent site in which ectopic liver tissue has been encountered is the bdominal cavity Thi applies both to cases in which the specimen is completely detached and to cases in which the ectopic liver tissue is attached to the liver by a pedicle

Both Thorsness [11] and Klein [7] found a microscopic fragment of ectopic liver in the wall of the gallbladder In both cases the fragment was located in the free wall of the gallbladder In a 12 year-old girl Pettersson [8] encountered a completely detached hepatic lobule the size of a grape-fruit in the retroperitoneal space Schnuder [9] and H ld & von Haam [5] described hepatic liver tissue that was found in the splenic capsule In both cases the fragment wa small Brühl [2] found ect pi liver tissue in the great omentum

Usually the presence f ectopi liver

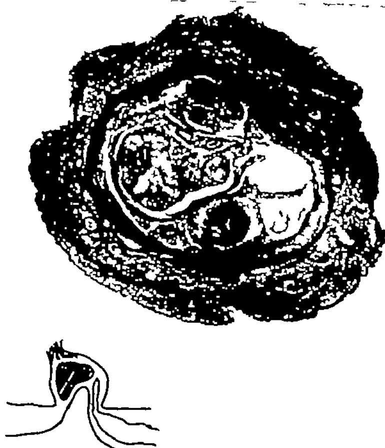


Fig. 2. Case 2. The schematic drawing depicts the operation. a.

tissue is noted as a secondary observation at autopsies. In the cases reported by Pettersson and Kaufman & Madoff the ectopic liver tissue resembled a tumor on account of its large size

In both my cases the ectopic liver tissue was located at the same site without any *connection to the liver itself* in the wall of a small omphalocele

In the first case the hepatic tissue encountered was quite immature Its histological structure was primitive (Fig 3) A small amount of connective tissue was present, and in addition there were signs of hematopoiesis in the liver

Further a structure resembling the gall bladder was present. In Fig 1 it is seen that the aberrant liver tissue was 'encapsulated' by the surrounding tissue.

In the second case a fragment of hepatic tissue was also encountered enclosed by an unattached capsule (Fig) The degree of maturity of this hepatic tissue is considerably higher than in the preceding case In Fig 4 various features characteristic of the liver are distinctly seen, such as the lobular structure biliary ducts and hepatic cell bridges. The proportion of connective tissue in the second case is greater than in the first



Fig. 3. Case 1. Hepatic tissue. The irregular structure of the liver is distinctly seen. 300.

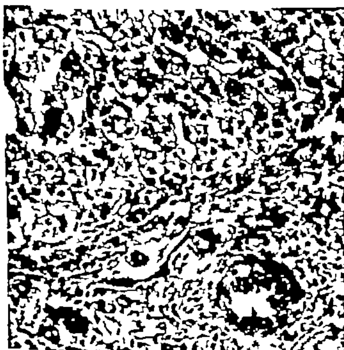


Fig. 4. Case 2. An abundance of hepatic cell bridges and biliary capillaries are seen. 300.

References to a free ectopic liver are rarely found in the literature Soper & Green [10] reported 19 cases of omphalocele, in three of which hepatic tissue was present in the malformation. However in these cases portions of the normal liver extended to the omphalocelic sac.

According to Bremer [1] and Willis [12], an omphalocele corresponds to the normal developmental stage of the embryo during the 6th to 12th embryonal week, when the entire foregut is to be found in a sac outside the abdominal cavity In the 4th embryonal week the liver gall bladder and intra as well as extrahepatic biliary ducts are formed out of a ventral distension of the foregut. The liver grows into the septum transversum, and at this stage relatively small amounts of connective tissue are present. In a later embryonal stage i.e. after 10 to 12 weeks, the intestines are retracted into the abdominal cavity

In Case I it is reasonable to assume from the immature structure of the liver fragment and the small amount of connective tissue contained in it that the portion of the liver which became ectopic remained outside the abdominal cavity at an early stage of development. In Case 2 the hepatic lobe might have become detached at a fairly late stage since features characteristic of the normal liver were manifest, as well as a fair amount of connective tissue

Summary

Two newborn infants are described, both of whom had a slight omphalocelic anomaly In both an ectopic lobe was completely detached from the liver itself and located outside the abdominal cavity In the first case the hepatic lobe had apparently become detached at an early embryonal stage since the histological picture of the liver was extremely primitive. In the second case the hepatic lobe was perhaps detached in a late intrauterine stage, as its histological picture was characteristic of the mature liver

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CASE REPORT

Generalized BCG Infection with Fatal Course in an Infant

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There is evidence that following BCG vaccination there occurs a hematogenous dissemination of BCG with formation of small regressive foci in many organs [1, 4, 15, 19]. Only very seldom does this dissemination lead to tuberculous disease and as only a few cases have been reported, one must assume that fatal BCG infection following vaccination is very rare indeed.

According to Wallgren [21] eight fatal cases are known to date. However, as one cannot take it for granted that all cases are recognized and reported, it is not possible to state an exact figure of frequency for fatal BCG complications. What is striking is that as many as four of the eight cases in which connection with BCG vaccination seems established are reports from the Scandinavian countries. The most likely explanation is that BCG complications have been given close attention in these countries. In Norway all BCG vaccinated persons are thus carefully followed and all instances of unusual postvaccinal reactions are reported to the public health authorities. All tubercle bacillus strains cultivated from previously BCG vaccinated patients with primary tuberculosis are furthermore examined with particular care. That grave postvaccinal complications should escape recording is, under the circumstances, highly unlikely and it seems justifiable to assume that such complications are not in reality more frequent in Scandinavia than elsewhere. In 1957 Horwitz & Meyer [6] calculated that the four Scandinavian cases had occurred among around 4 million persons vaccinated. The present case included, there are at present five known cases in Scandinavia and the number of persons vaccinated is estimated to be between 6 and 7 millions. The probable incidence can thus be put at less than one case per million vaccinated.

Case Report

In the Pediatric Department of Oslo University Hospital a fatal case of generalized BCG infection in an infant has recently been observed. The patient was a girl, born on September 26th, 1960, who was admitted to the Hospital on March 29th, 1961 and died on April 19th the same year. Her mother was treated for pulmonary tubercu-

losis in a sanatorium from April to October 1960 He presented an exudative outbreak of an old, previously inactive process and drug therapy gave satisfactory results. Tubercle bacilli cultivated in various samples of sputum and larynx smears were sensitive to streptomycin, isoniazid, and PAS.

The family's first child a boy born in 1955, died at 5 months f age following 2 months hospitalization. Prior to admission he had at times suffered from diarrhoea. He had not been BCG vaccinated and nothing is known as to his tuberculin reaction. The hospital diagnosis was erythrodermia desquamativa and acute suppurative otitis. It is of particular interest that on electrophoresis his serum proteins were found to be normal. Autopsy revealed enteritis, generalized exanthema, bilateral otitis media, and bronchopneumonia.

The family's second child, a girl born in 1956 died at 5½ months of age after one week hospitalization. This infant too had previously had attacks of diarrhoea and vomiting; in addition she had at times been febrile, and had coughing bouts, dyspnoea, and cyanosis. During hospitalization she showed symptoms of heart failure The clinical diagnosis was congenital heart disease; myocarditis. There is no information on BCG vaccination or tuberculin reaction. Autopsy was not done.

The third hild, a girl born in 1959 is in good health She was BCG vaccinated in June 1960 The postvaccinal course was uneventful and she became Pirquet positive.

The patient was the family fourth child. She was born at term following normal pregnancy Del very was normal and there were no neonatal complications. Birth weight was 4050 g From two weeks of age the patient suffered from oral moniliasis.

Adrenalin Pirquet test was done t six weeks of age Examination two days later showed negative reaction, and the patient was BCG vaccinated with intracutaneous application. Radiological examination had not been made. On follow up 8 weeks later the adrenalin Pirquet reaction was still negative, but revaccination was not done.

No signs of local or regional complications like ulcerations, adenitis etc. were observed. Two days after vaccination the patient developed catarrhal symptoms, with coughing, nose secretion, and subfebrile temperature. In addition she had periodic attacks of diarrhoea and the marked oral moniliasis persisted.

At five months of age the patient was admitted to the local hospital. Bilateral otitis media and extensive white coating on the mucous membrane of the mouth were demonstrated. Apart from this, clinical examination revealed nothing special. It should be noted that microscopy f feces showed fat in abundance. Total serum protein was 6.6 g/100 ml; electrophoresis showed reduced albumin fraction significantly increased $alpha_1$ and $alpha_2$ globulin, while gamma globulin was not demonstrable The t berculin reactions (Pirquet and Mantoux) were negative. Radiological examination of the lungs showed nothing pathologic

The patient was treated with paracentesis, antibiotics and antimycotics. There was rapid improvement of the ear disease while the infant's condition was otherwise unchanged until a marked deterioration occurred after two weeks hospitalization. At this time the patient developed fluctuating septic fever and the number of leucocytes in the blood rose from 12 000 to 31,500/mm³ with marked shift to left. Clinical examination revealed an approximately orange-sized, firm, irregular tumor in the left hypochondrium toward the midline. The tumor seemed attached to the posterior abdominal wall.

On admission to the Pediatric Department the above-mentioned clinical findings were confirmed The patient was febrile with a rectal temperature of 38.7°C. Hemoglobin was 8.7 g%, erythrocytes 2.84 mill./mm³ leucocytes 26,700/mm³ with marked shift t left. Hematocrit 35. Sedimentation rate 14 mm. The urine contained albumin. Spinal fluid was normal, a was bone marrow and several blood cultures were negative Microscopy of feces showed abundant neutral fat. Total serum protein was 6.5 g/100 ml, al-



Fig. 1 The duodenal loop is considerably widened indicating an expansive process in the pancreatic region.

bumin 2.7 g, lpha$_1$-globulin 0.8 g alpha$_2$-globulin 1.2 g beta-globulin 0.8 g, gamma-globulin 1 0 g. Re-examination shortly before death showed total protein 4.1 g/100 ml, albumin .6 g, alpha$_1$-globulin 0.5 g, alpha$_2$ globulin 0.5 g, beta globulin 0.3 g and gamma-globulin 0.2 g

Radiographs of the lungs revealed nothing pathologic Urography disclosed slight lateral displacement of the left kidney without pelvic defects. Radiographs f the stomach, duodenum and intestines showed hat the duodenal loop was markedly widened indicating an expansive process in the pancreas region (F g 1)

The patient was treated with blood transfusions, iron, sulfonamide penicillin, streptomycin, and subsequently chloromycetin. The oral mucou membrane wa treated with mycostatin and gentian violet. During the first week f hospitalization she was subfebrile later again highly febrile with fluctuating septic fever

After three weeks hospitalization the abdominal tumor was suddenl no longer palpable A new series f radiograms howed



Fig. — The duodenal loop is smaller than at the first examination (Fig. 1), but still not normal.

that the widening of the duodenal loop was considerably reduced (Fig. 2) The jejunal and, to some extent, ileal mesentery looked shrivelled, so that the intestinal loops pointed radially to a centre in the pancreatic region (Fig 3). This seemed t indicate pancreatitis and secondary shrinking Examination f serum amylase and diastase in the urine revealed normal values.

From this time the patient condition grew rapidly worse. Extensive edemas, icterus, and an intractable state f shock developed. Treatment with intravenous fluid, plasma, blood and corticoids was without effect, and the patient died after recurrent attacks of severe general convul sions.

Autopsy findings

The patient was a 7-month-old girl, 67 cm in height and 6450 g in weight There was marked icterus and the abdomen appeared dilated. The lungs (the right 70 g, the left 60 g) were somewhat firmer than usual, "fleshy" on section with a little reddish mucus in the small bronchi. In the lower part of the bdomen the peritoneum was smooth, shiny and reflecting, but in the upper part there was a fibrinous, fat layer on intestines, intestinal mesentery and the parietal peritoneum. There were 150 ml clear yellow ascites. The liver weighed _50 g It was a greyish-yellow and both surface and cut showed numerous, diffusely scattered purple spots, ranging from pinhead sized t grain-sized.

In the area before the pancreatic head was a small hen egg-sized prominence to which the duodenum, kidneys, and adrenal glands were adherent There were however clear lines between these organs and the tumor on the cut surface. Section showed that the



Fig. 3. The mesentery of the jejunum and, to some extent, of the ileum is contracted so that the intestinal loops point radially t centre. The picture indicates shrinking process in the root of the mesentary

tumor consisted of a partly fluid caseous substance of greyish yellow A sample of this substance was sent for bacteriological examination.

The spleen weighed 0 g The capsule was somewhat wrinkled, and on the cut surface were numerous small whit nodules f up t grain size and few slightly larger nodes resembling small abscesses.

N changes were found in the mucous membrane of the small intestine and there were no demonstrable ulcerations or scars. However mentioned above the upper part f the intestinal mesentery was coated with fat adherences. N other pathological findings were revealed on macroscopic examination.

Microscopic examination revealed that the tumor in front f the pancreas consisted of markedly dilated lymph nodes haracterized by central necrosis of larger and smaller nodes. The necrotic area were limited by a border f juicy specific granulation tissue with epithelioid cells, few Langhans giant cells, and numerous lymphocytes, but no fibrosis. Special staining brought out myriads f acid fast rods resembling t bercle bacilli in the necroses and gran lation tissue (Fig. 4).

Similar hanges, with large quantities f acid fast rods, were found in the spleen,



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Autopsy findings

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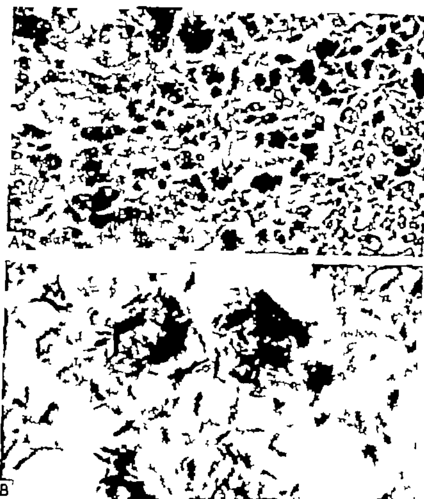


Fig. 4. *A* Histological section from the rand zone of small liver necroses. Note the faint cellular reaction. About 300 *B* Large number of acid fast rods in the necrotic areas. *Ziehl* Neelsen stain. About 1000

pancreatic and renal capsules, both adrenal glands, lungs, and liver. The brain was examined by a neuropathologist (Dr Christie Löken). Meningitic changes and degenerative changes of the cerebral cortex were demonstrated, but these were not definitely of specific nature.

Pathologic-anatomical diagnosis Disseminated tuberculosis.

Bacteriological examinations

The specimen sent from the post mortem examination of the patient consisted of caseous material from the mesenterial glands.

Gram-staining showed no bacteria but scattered throughout the smear were indistinct gram positive irregularly formed dots and streaks. Staining by the Ziehl Neelsen method revealed swarm of acidfast bacilli arranged in cord.

Cultures on ordinary bacteriological media were negative. Cultures on Lowenstein's medium after about three weeks gave growth of colonies which were

TABLE 1 *Sensitivity determinations to drugs*

	µg per ml				
	50	10	3	1	0.5
Streptomycin	—	—	—	—	
PAS	—	1		4	
Isoniazid	—	—	—	—	—

1 Few colonies. 2: Several colonies. 3: Nearly full growth. 4 Full growth (as in control tube).

indistinguishable from colonies of tubercle bacilli of the human type

Five guinea pigs were inoculated in the groin. None of these died of tuberculosis, nor did they show signs of disease other than a local reaction in the form of an infiltration at the site of injection and moderate regional gland enlargement. These changes disappeared after some weeks.

Zero point five ml tuberculin given subcutaneously after _ months killed 2 of the 5 inoculated animals. These animals ere examined post mortem but no changes were found. Smears from the spleen and the liver stained by the Ziehl Neelsen method showed acidfast rods, and cultures from these organs on Löwenstein medium gave growth of colonies which resembled those with which the nimals had been inoculated. The 3 guinea pigs which did not die after tuberculin injection were still live after 5 months. During this time tuberculin was given subcutaneously three times, but none of these animals died

The results of the sensitivity determinations *in vitro* to drugs are given in Table 1

Cat lase activity test [1_], neutral red test [ ], peroxydase test and niacin test were performed with the acid fast bacilli isolated from the specimen a strain of mycobacterium tuberculosis (human type), a strain of *mycobacterium bovis* and a strain of BCG The results of these tests are given in Tabl _

TABLE _ *Biochemical reactions of patient's stra n in comparison with standard strains*

	Cata lase	Per oxy dase	Neutral red	Niacin
Patient strain	+		yellow	—
BCG	+	—	yellow	—
M. tuberculosis	+ —	+ —	red	+
M. bovis	+ +	+	red	—

Thus the patient s strain could not be distinguished from BCG on the basis of these examinations Microscopical exa minations of the cultures showed typical cord formation. Examination of pathogenicity in guinea pigs showed no spontaneous death within 5 months although the animals did develop tuberculin allergy as shown by the fact that two of the five animals died of tuberculin shock. Post mortem examinations of these two guinea pigs revealed no changes in the animals. Cultures from the spleen and liver on the other hand gave good growth of acid fast rods on Löwenstein s medium.

When a freeze-dried culture of the same batch of BCG as was used to vaccinate the patient was made available to us, all these tests, together with additional tests in guinea pigs were repeated with the BCG strain contained in the latest batch of BCG vaccine a human strain, and a b ine strain included for comparison Again the patient strain wa indistinguishable from the BCG strains

The patient strain was also examined

by Professor K. A. Jensen, Universitetets Institut for Almindelig Patologi, Copenhagen [8] by Professor P Oeding Gade s Institute Bergen [13] by Dr Arne Lind, Gothenburg [9] and by Mr K. Lindqvist, The Veterinary Institute Oslo [10] The results of all these examinations confirmed the conclusion that the patient s strain was indistinguishable from BCG

The BCG vaccine

The Norwegian BCG Laboratory produces and distributes fresh liquid vaccine every week. Since 1953 the Swedish BCG substrain from the Calmette Laboratory in Gothenburg has been used exclusively in all routine vaccine production.

The BCG strain is maintained by alternate cultures every 14th day on bile potato and Sauton potato and the vaccine suspensions are prepared from 10-day-old surface cultures on Sauton liquid medium. The employd suspension fluid consists of diluted Sauton and the concentration of the standard vaccine for intracutaneous injection has been 1 mg semi-dry culture mass per ml. The vaccinal dose is 0 1 ml vaccine.

All batches of vaccine are controlled with reference to content of viable BCG units. The determination is done by dilution of the vaccine inoculation on the Löwenstein-Jensen medium and counting of colonies, after standardized method. The vitality of the cultures is examined by measuring the oxygen consumption per time unit in the Warburg apparatus. The potency of the vaccine, the local reactions and the postvaccinal tuberculin allergy are examined by inoculation on guinea pigs according to the Jensen method. The innocuity of the vaccine is controlled on guinea pigs.

In the five-year period 1957–61 the average number of viable BCG units in the Norwegian vaccine has been found to be 28 million per ml and the average oxygen consumption in the Warburg apparatus is estimated at 98 $\mu l/60$ mg/hour On guinea pigs the average postvaccinal Mantoux reaction with 1 mg tuberculin has been 10×17 mm and in all animal experiments the BCG strain has proved to be stable and non pathogenic in guinea pigs.

The vaccine used in the case described, No B-189 was produced on November 2, 1960 Nothing unusual was observed in the culture s appearance or growth conditions, and the standard method of production was employed. Laboratory controls revealed that the vaccine contained 31 million viable BCG units per ml, with an oxygen consumption of 101 $\mu l/60$ mg/hour The Mantoux reaction in animal controls was 20×18 mm, and autopsy of the animals after 3 and 6 months revealed normal conditions.

Since the laboratory started to make use of the Swedish BCG substrain no change in the strain s properties has been demonstrable through laboratory controls or animal experiments. Nor have the routine control vaccinations, done by the National Institute of Mass Radiography with all batches of vaccine shown changes in the vaccine s properties as measured by the postvaccinal tuberculin allergy and the frequency of unwanted reactions. According to reports about 80 000 persons have been vaccinated per year giving a total of about 650 000 persons vaccinated during the period 1953 to 1961 The present case excluded, no case with grave complications has been reported

With reference to the present batch of

vaccine a total of 231 ampoules has been distributed to 201 vaccinators. The vaccine has been used in about 900 vaccinations and no other case with complications has been observed. The vaccine ampoule employed in the present fatal case was also used on two other patients born in 1938 and 1940 respectively The post vaccinal course was normal without complications in both these patients. They were re-examined one year after vaccination (October 1961) and presented normal findings.

On the basis of the reported observations one feels justified in concluding that the fatal complications in the present case cannot be ascribed to peculiarities in the BCG strain employed, nor to special properties in that particular batch of vaccine.

Comments

In 1953 Meyer [11] described the first fatal case of BCG infection in Denmark. The patient, a previously healthy boy was BCG-vaccinated at 7 years of age After one month he developed a local glandular abscess and later a generalized swelling of the peripheral lymph nodes. After a further six months he became feverish and died cachectic 2 years after vaccination. He had shown no sign of reduced resistance to infection prior to BCG vaccination.

In 1954 Thrap-Meyer *et al* [14 17 20] reported the first Norwegian case This was a young man who was BCG vaccinated at 19 years of age. Prior to vaccination he had had a persistently increased sediment ation rate about 40 mm and it is possible that his resistance to infections had been generally reduced from childhood on A year after vaccination a regional suppurative adenitis developed After another year he developed an abscess in the thoracic wall. In spite of treatment with streptomycin, PAS and INH foci developed in lungs kidneys and several bones. The patient died cachectic 5 years following vaccination.

There are two Swedish reports of fatally ending generalized BCG infection following vaccination in infancy i.e. Hollström & Hård [5], and Falkmer Lind & Ploman [3] Both patients were vaccinated shortly after birth and developed symptoms of generalized infection 6 months later Autopsy revealed extensive changes in various organs. Our patient was vaccinated at 6 weeks of age and developed severe symptoms of infection 4 months later In this case too autopsy showed marked changes in many organs the most note worthy of which was the considerable mesenteric glandular affection. The pathologic-anatomical changes in these three patients have several points in common They all present the features which seem to characterize BCG infection i.e. little tendency to tuberculoid structure and myriads of acid fast rods in the affected areas (Fig 4) A marked caseous necrosis as in the present case has also been demonstrated in most of the fatal cases described.

In severe complications following BCG vaccination it is natural first of all to suspect the vaccine Account has already been given of vaccine production in Norw y in general and of the batch employed i particular N evidence that in creased virulence or other hanges in th BCG vaccine might explain the complica tion has ever been found. nd one is of

the opinion that *such a possibility* can be disregarded in the present case too

Two of the patient's three siblings died at an early age Both had previously shown definite signs of reduced resistance to infection, and both probably died from infections. Adding this to the patient's case history one feels justified in concluding that a familial resistance impairment is present, apparently both to banal and specific infections. From the available data however it is not possible to come closer to an explanation of what causes this deficiency At the first determination of serum proteins the patient apparently lacked gamma globulin, at the second values were normal, and shortly before death values were reduced. The significance of the varying findings is hard to *evaluate Even if gamma globulin* deficiency can hardly be ruled out with certainty this explanation seems improbable. The brother who died at 5 months of age is reported to have had normal serum protein values. In Thrap-Meyer's case [17] markedly increased serum gamma globulin values were demonstrated.

It is typical of fatal BCG infection that the tuberculin reactions are weak or negative and that marked local adenitis develops following vaccination [6 18] Our patient was tuberculin negative on repeated examinations, on the other hand she never presented a clinically demonstrable local adenitis.

The important problem of why generalized BCG infection following vaccination develops in extremely rare individual cases is still unsolved and, with the data available today it seems doubtful whether one can find a common cause at all. In some cases more or less obvious signs point to reduced resistance to infection, in other cases such signs are lacking since the patient has previously reacted normally to common infections. A non fatal case of lupus vulgaris and multiple bone affections following BCG vaccination has previously been reported from the Pediatric Department [7 16]. This patient presented normal serum gamma globulin values It was supposed that the main reason for the hematogenous dissemination in this case was a transient reduction of resistance due to measles

Since the causal connection is none too clear one can do little to avoid the serious BCG complications It is possible that one should hesitate to vaccinate individuals who have previously shown definite signs of reduced resistance to infection. Vaccinated *children who have not had the* measles should be protected against such infection in the postvaccinal period.

That BCG inoculation has a protective effect against development of tuberculous disease is beyond doubt and every year numerous new cases can be prevented by vaccination Serious complications following such vaccination are extremely rare and give no ground for objecting to continued BCG vaccination [6].

Summary

A fatal case of generalized BCG infection following vaccination is reported. The patient, a girl BCG vaccinated at the age of six weeks, developed septic fever and leucocytosis at 5½ months of age and died at 7 months of age in a poor condition with extensive edemas icterus and severe attacks of general convulsions.

Autopsy revealed disseminated tuberculosis. The histological picture showed

little tendency to tuberculoid structure marked caseous necrosis and myriads of acid-fast bacilli in the affected areas. By bacteriological examination the acid fast bacilli were indistinguishable from BCG

Increased virulence or other changes in the BCG vaccine which might explain the fatal complication has not been found.

Two of the patient's three siblings had previously shown definite signs of reduced resistance to infection, and both died at an early age from infections. Adding this to the patient's case history one feels justified in concluding that a familial resistance impairment to infection is present. The cause of this deficiency is discussed.

There are at present five known cases of fatal BCG infection following vaccination in Scandinavia and the number of persons vaccinated is estimated to be between 6 and 7 millions. The probable incidence of fatal complications can thus be put at less than one case per million vaccinated.

As the protective effect of BCG vaccination is beyond doubt and the serious complications extremely rare there seems to be no ground at present for objecting to continued BCG vaccination

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CASE REPORT

Infantile Chronic Necrotizing Encephalopathy[1]

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Among the progressive neurological disorders in infancy and childhood one group is made up by diseases occurring in children said to have developed normally until the age of 1 to 2 years. Belonging to this group of progressive disorders are the leucoencephalopathies, the globoid cell type of Krabbe, the metachromatic type of Greenfield, and other even less commonly occurring diseases such as the pollody strophy the Hallervorden-Spatz disease the sclerotising leucoencephalopathy of van Bogaerts, some forms of amaurotic idiocies, the Louis Barr's syndrome and others.

Sometimes a brain biopsy perhaps in connection with a ventriculography may enable the clinician to make the correct diagnosis during the course of the disease but most often the diagnosis can be made possible only after a detailed brain autopsy is performed.

In 1956 [ ] the authors published a report on 'Combined Lesions of Basal Ganglia Medulla Oblongata and Spinal Cord in a 10 Year Old Boy Recently we have studied another case similar to the first one reported and present in the following the findings of this second case

Case report

Girl K.B.N (Case record no 583/35, Rigshospitalet, Pediatric Department).

Family history: No neurological diseases in the family Siblings: Two older siblings are normal. A third child was stillborn, the umbilical cord around its neck.

Pregnancy and delivery normal. Birth weight 4375 g Except for some unstable movements of the eyes there were no neonatal symptoms.

Her motor development was slightly retarded, and she was admitted to the local hospital when she was 8 months old. A diagnosis of congenital heart disease was made. When two years old she walked without support, at the age of 2 years and 8 months she had a head injury with a possible mild concussion. Two weeks later it was noticed that she was losing her physical abilities, and shortly afterwards she had spells with pallor and crying She was then admitted for the first time t the Pediatric Department

When she was almost 3 years old physical examination t the time of admission revealed a rather inactive girl. The heart examination showed voussure and strong systolic murmur supported the diagnosis of a ventricular septal defect. She could speak only a few words but understood most of what was said to her It was necessary to support her in both sitting and standing

[1] This study was supported by PHS Research Grant B-2408 from The National Institute of Neurological Diseases and Blindness, Bethesda, U.S.A.


Fig. 1. Ventriculography at the age of 3 years showing moderate symmetrical dilatation of the ventricular system (ratio 0.34).


Fig. 2. Lumbar pneumoencephalography at the age of 7 years showed unchanged conditions.

positions. There was a slight left-sided paresis with considerable hypertonicity in all four extremities, the tendon reflexes were brisk and the plantar reflexes normal.

During her stay in the department a number of examinations were performed, including examination of the spinal fluid and EEG both with normal findings. She was admitted to the Neurosurgical Department of the Rigshospital and a ventriculography was done showing a moderate symmetrical dilatation of the lateral ventricles (ratio 0.34), the width of the 3rd ventricle being 10 mm (Fig. 1).

While in the department her condition improved. This improvement continued during the following years, and it was noted that she talked fluently 5 years old.

When she was 6 years old the neurological examination was dominated by pyramidal signs with general spasticity and bilateral Babinski. There was still slight left sided hemiparesis as well as some difficulty coordinating the movements of the hands.

She was re-admitted to the Pediatric Department when she was 7 years and 2 months old because of lack of development. Her speech had become difficult to understand. Eye examination revealed nystagmus and alternating convergent squint. The pyramidal symptoms were now combined with extrapyramidal symptoms in the way of pronounced rigidity.

EEG had changed since the first examination and now showed severe dysrhythmia. Spinal fluid was normal and PEG was unchanged: Ratio: 0.34 (Fig. 2).

During the following years her condition improved somewhat up to the age of 10, at which time she started to have seizures of petit mal type which only responded partially to adequate treatment.

From the age of 11 her rigidity became much worse and she was no longer able to use her right hand when eating. From this age onwards she started to have episodes of fever of unknown cause lasting up to two weeks and similar episodes continued to occur until her death.

When admitted the last time to the Pediatric Department she was 11½ years old. She was now unable to talk, and was more inactive than before. There was marked rotatory nystagmus and convergent squint

Hypertonicity was only moderat in the upper extremities, but marked in the legs. The increased tendon reflexes were less dominant and th plantar reflexes were normal. It was noted that occasionally she had rhythmic movements of the shoulder muscles on the left side. The diagnosis of a congenital heart disease was now very much doubted by the cardiologist, who found that neither the murmur nor the ECG and X ray supported this diagnosis.

Before and after this admission she spent a great deal of her time at a home for spastics, and although her condition during the following years got worse she was still able to read books written for her age (Fig 3).

The seizures increased in number and she had a few grand mal convulsions.

The general hypertonicity was present all this time, the tendon reflexes changed somewhat and became brisk as before. She developed contractures of the knees in spite of physiotherapy A number of different drugs were given in order to reduce her hypertonicity On several occasions she



Fig 3 The patient t the ge of 12 years

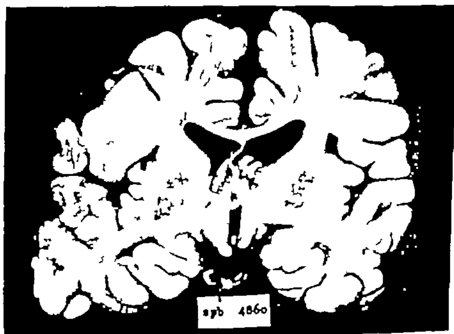


Fig. 4. Coronal section of the brain showing the marked alterations in the putamina and in the caudate nuclei.

a



b



Fig. 5 (a) Lower part of the putamen showing necrotizing degeneration with astrocytic proliferation, macrophages and thickening of the vessel walls. The ventricular part of the putamen is to the right. H.-E. × 10. (b) The same with the necrotizing area to the left. Note the increased number of fibrillary astrocytes and macrophages. H.-E. × 40.



Fig. 6. ( ) Upper cervical segment of the spinal cord with degeneration of the grey substance of the anterior horn. There is edema, hyperemia and macrophages. H E. 10 (*b*) Part of the

reacted too much with drowsiness and perhaps hallucinations. These unfavourable reactions rapidly disappeared when the dosage was decreased or the drug withdrawn.

Three months prior t her death she had respiratory difficulties which became g gravated, she was treated with tracheotomy and died 2 weeks later in hyperpyrexia at the age of 13 years and 10 months.

During her disease a great number of laboratory studies had been performed and only few abnormalities found The sedimen tation rate was increased in the beginning of her disease later on normal. Serum proteins and lipids were normal, and liver function as normal too.

EEG with the exception of the first one was severely abnormal and in the later years showed petit mal picture

The spinal fluid was last studied during her admission when 11 years ld and was found normal with regard to content of electrolytes and proteins.

Autopsy

The post-mortem examination revealed scattered bronchopneumoniae on both sides, and moderate acut stasis of the liver and the spleen. N bnormalities were noted on the examination of the heart.

Brai autopsy

Brain weight after formalin fixation was 1800 g. Coronal sections showed moderat symmetrical dilatation of the ventricular system and symmetrical sharply outlined necrotic areas occupying both putamina. The caudat nuclei were trophic, whereas the internal capsules, the hypothalamus and the globus pallidus were macroscopically normal on both sides (Fig 4)

In the brain stem the tissue ppeared grey yellow and soft in the ventricular parts of pons and medulla oblongata; cerebellum was normal. *Histological examination* revealed no chronical lesions in the cortical grey matter but anoxic changes with acut shrinkage of the nerve cells and their nuclei. N myelin degeneration occurred in the whit matter of the cerebrum.

In the caudat nuclei few nerve cells are preserved in the peri entricular areas and the ependymal cells are normal. Otherwise there is complet degeneration of the nerve cells both here and in the putamina (Figs. 5a, 5b). The remaining tissue consist of fibrillary astrocytes and vessel with thickening of the walls, but without obliteration of the lumina. There is n irregular xtension of the process into the internal capsules on both sides, only minimal involvement of the globus pallidus on one side no involvement was seen of the thalamus, the substantia nigra, the hypothalamic nuclei or the red nuclei. The examination of the brain stem show subacut and acut degeneration in the periaqueductal tissue and in the periventricular part of pons and medulla with preserved ependymal cells.

The reticular formations are involved but in the nuclei mbigu and the hypoglossal nuclei only a part of the nerve cells are destroyed. No bnormalities are found in the medial lemnisci, the spinal tracts of the trigeminal nerves, the restiform bodies the pyramidal tracts or in the oliva

The cerebellum is histologically normal

From the spinal cord only the two upper cervical segments have been removed and degeneration is found in the grey matter similar to the degenerative changes in the medulla (Fig 6a, 6b)

It must be emphasized that the leptomeninges were thickened, especially on the surface of the brain, and that a slight degree of infiltration with lymphocytes and macrophages occurs. In the brain tissue no cell inf ltration is seen.

Histological diagnosis. Infantile chronic necrotizing encephalopathy

Discussion

The clinical picture in the case reported is characterized by a progressive extra pyramidal and pyramidal encephalopathy beginning at the ge of two years and lasting almost 1 years. The pathoana tomical findings are macroscopically and

histologically so characteristic, with the symmetrical degeneration of the putamina and the caudate nuclei and with involvement of the brain stem and spinal cord, that one would expect to find a number of similar cases in the literature but this is not so One reason may be that it is difficult to identify these cases as long as an adequate name has not been suggested.

It is possible that some cases have been described under pathoanatomical names such as status marmoratus and status dysmyelinatus (Vogt & Vogt [11]) because the localisation of these brain lesions is the same as in our case A large series of these cases has been published by Kraemer [7] of 19 patients with the diagnosis of status dysmyelinatus and 79 patients with status marmoratus The average lifetime was in the first group 7.2 and in the second group 14.6 years In 30 cases the etiology was perinatal injuries and in most of the other cases severe diseases during infancy No detailed information was given of the clinical course

The brain lesion in the basal ganglia found in our case is identical with the lesion found in cases of hepatolenticular degeneration (HLD Wilson s disease) but in such patients a disturbance in the copper metabolism is found both in the brain and in the liver We have no studies of the copper metabolism in the present case but the liver function was normal and at autopsy the liver showed no alterations Because of the normal liver Wilson s pseudosclerosis and the neurological disorders caused by liver diseases other than HLD (Eicke [4]) can also be excluded In the literature one case is described with a clinical picture resembling that of Wilson s disease, but with no involvement of the liver at autopsy (Deberdt Radermecker & Guazzi [3]) The case described by us [2] showed a clinical as well as a pathoanatomical picture with a striking similarity to the present case. The boy described developed at the age of two years a slight right-sided hemiplegia of unknown etiology His symptoms progressed and were characterized by dystonia and pronounced dysarthria, his intelligence seemed almost undisturbed. He died suddenly after a few hours of hyperpyrexia when 10 years old PEG performed three times revealed a moderate symmetrical dilatation of the ventricular system ratio 0.36 The brain autopsy showed a symmetrical degeneration of the caudate nuclei and the putamina that had existed for several years, whereas more recent lesions were found in the brain stem and spinal cord. In the discussion of the case references can be found to diseases affecting the basal ganglia and it was concluded that no identical case could be found in the literature

Symmetrical lesions of the basal ganglia and mesencephalon in children have been described by Verhaart [10] in Chinese infants. These children were all less than one year old and the duration of the fatal disease was extremely short only a few weeks.

Since Leigh [8] described subacute necrotizing encephalomyelopathy in an infant and later Feigin & Wolf [5] published three cases of a disease in infants resembling chronic Wernicke encephalopathy a few report have appeared (Richter Cases and 3 [9], Ford [6]; Brandt & Olsen [1]) in which the lesions involve the basal ganglia besides the midbrain and particularly the cerebellum

(D) Paroxysmal nocturnal hemoglobinuria. In subgroup A they include cases with isolated hypoplasia of the megacaryocytes and cases with more extensive bone marrow hypoplasia as well.

It is often maintained that in congenital hypoplastic thrombocytopenia only few if any megacaryocytes are found in the bone marrow. However, Nilsson & Lindholm [11] in two typical cases, in which bilateral aplasia of the radius was also present, found normal or nearly normal amounts of megacaryocytes. But these cells looked relatively immature and inactive.

It is reasonable to class our three patients as cases of congenital hypoplastic thrombocytopenia, and thereby accept that in this condition increased numbers of megacaryocytes with reduced thrombocytopoietic activity can occasionally be present in the bone marrow. We must also believe that congenital hypoplastic thrombocytopenia in some cases may be due to a hereditary defect in the megacaryocyte population, a fact which has not previously been known. For these cases the term *hereditary hypoplastic thrombocytopenia* is proposed.

Summary

Three patients, a mother and two sons, suffering from thrombocytopenic purpura due to deficient production of blood platelets are presented. The disease is thought to be of genetic origin and is called hereditary hypoplastic thrombocytopenia.

The number of megacaryocytes was normal or most often moderately increased in the bone marrow, but signs of active platelet production were scarce. The platelet survival determined by means of radiochromium was found to be normal. Platelet antibodies could not be demonstrated (only one of the cases studied). Treatment with corticosteroids or with a combination of anabolic steroids and corticosteroids seemed to be ineffective. In one of the cases splenectomy was performed. A transient normalization of the platelet count was obtained, but the bleeding tendency soon recurred and the patient died, possibly from a pneumococcal infection. In one of the patients certain concomitant malformations were present (bilateral aplasia of the twelfth rib, mild hydronephrosis on the right side). The condition can be regarded as a subgroup of the congenital hypoplastic thrombocytopenia.

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Family Background and State of Mental Health in a Group of Diabetic Schoolchildren

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In the day to-day management of diabetic children and adolescents many problems are met with. As in the treatment of other chronic diseases during growth, the child s adjustment depends a great deal on its own personality and environmental background. The interaction of these factors and the diabetic state has been the subject of various types of investigations. However many of these involve only a few extreme cases and even when larger series have been gathered they are seldom non-selective conclusions thus being without general validity

The present study was undertaken to find out whether diabetic children have an enhanced frequency of emotional disturbances and, if so, what factors in the diabetic state might have influenced the symptoms.

M terial and Methods

During the autumn f 1959 all school nurses in Stockholm were requested through the principal school medical officer (Dr U Hjärne) to report all cases f diabetes mellitus in the schools. The material was completed by the author in the spring f 1960 by means f a similar request t all privat schools and by reviewing all records on diabetics kept by the out-patient departments of the four children hospitals in Stockholm in order to include the year olds beginning school in the autumn term of 1960 By studying the school health cards of the diabetics, a person conversant with such work selected a control group consisting of non-diabetics of the same sex, age and school class, whose fathers had similar employment to that f the fathers of the diabetic "twins" It was also ttempted t match the pairs as losely as possible with regard to number of siblings, position in the family and dwelling standard. The first subject fulfilling or coming nearest to fulfilling these requirements was chosen as the control. If none was considered suit ble or f the selected non-diabetic refused t co-operat no attempt was made to find another

The material thus obtained is presented in T ble I. Ten cases were not traced in time to receive the necessary instructions before the beginning of the study and 32 did not want to participate. A further 7 had to be rejected because of the mothers lack of time or acut illness at the time f the interview given by the author at the end of the observation period. The final groups thus comprised 145 (91.2%) diabetics and 126 (87.5%) non-diabetics. Matched into pairs were 238 cases (114 ♂ 124 ♀) Eleven of the 14 diabetics who refused to co-operat were aged 15 or more 4 f the 6 boys were in their final class at school. Some f the girls parents gave as a reason for refusal to participat the wish t conceal the disorder

TABLE 1 *Composition of material*

	Diabetics			Non-diabetics		
	Boys	Girls	Total	*Boys*	*Girls*	*Total*
Primary material	5	90	165	72	82	145
Cause of rejection:						
Not traced	1	3	4	5	1	6
Unwilling	6	8	14	6	12	18
Mothers not interviewed	1	1	2	1	4	5
	8	1	20	12	13	25
Final material	67	8	145	60	66	126

Sex and age

The distribution of sex and age is to be found in Table 5. In 44 of the 119 matched pairs (18 ♂ 26 ♀) the 'twins' were not born the same year. Sixteen of these pairs were aged 15 or more. In 8 pairs (8 ♂ 10 ♀) the age difference exceeded 12 months, the highest value being 20 months.

Social groups

The cases were classified into social groups (I, II or III) based on the occupation of the parent as recorded on the child's health card and on additional information obtained at the interview. The register of occupations used by the Central Bureau of Statistics in its reports on election returns in Stockholm served as a guide. The distribution as presented in Table 2 showed a good correspondence between the whole diabetic and non-diabetic series. When moving to higher grade schools a form of social selection usually takes place and, in order to be able to compare directly the diabetics distribution with that of the election returns, the occurrence of the various social groups in the diabetics 8–14 years old (68 cases) was calculated. This particular age range was chosen because all diabetic children belonging to it would have been registered (15). The social grouping obtained in this way was identical with that met with in Stockholm in general. It was impossible to achieve full agreement as regards the fathers employment in 20 pairs (22 ♂ 18 ♀). In 19 cases the diabetics fathers belonged to a higher social group than the non-diabetics but in no instance was the step greater than of one group.

Size of family

The mean number of children per family was for boys 2.5 for the diabetic and 2.4 for the non-diabetic, and for girls 2.4 and 2.1 correspondingly. The frequency of only children among the diabetics was 15.9% (9 ♂ 14 ♀) and among the non-diabetics 16.7% (7 ♂ 14 ♀). In 66 of the matched pairs both the number of children per family and the child's position in the family corresponded. In the 53 remaining pairs an only child was compared with a child from a larger family in 12 instances, the diabetic being the only child in 8 pairs.

Dwelling standard

Two classes of dwelling standard were considered. The limit for overcrowding was set according to Roos (23) who regarded flats with more than 1½ persons per room as overcrowded, children counting as one person. The frequency of overcrowded homes was 35.3% (5 cases) among the diabetics and 29.4% (27 cases) among the non-diabetics. The diabetic child from an overcrowded home was in 11 instances compared with a non-diabetic from a home with satisfactory standard. The reverse situation was found in 9 pairs.

TABLE 2. *Distribution of the material in social groups*

Social group	Diabetics		Non-diabetics	
	n	%	n	%
I	18	12.4	10	.9
II	67	46.2	61	48.4
III	60	41 4	55	43 7
Total	145	100.0	126	100.0

Civil status of parents

The above requirement in themselves afforded much difficulty to the finding f suitable so-called "social twins" and it was therefore impossible t attain full correspondence as regards civil status of the parents (verified for the non-diabetics in the census list) Of the matched pairs, 9 diabetic and 5 non-diabetic children came from broken homes due t divorce and 7 and 2 respectively from homes broken because of the death of one f the parents. In the final diabetic group there were 22 instances f broken homes (15.2%) and in the non diabetic 9 (7 1%) ($p < 0.05$) The frequency f broken homes in the primary material, i.e. rejected cases now included, was 14.5% (23/163) in the diabetic group and 10.3% (16/155) in the non-diabetic, a statistically insignificant difference

Mother's employment

Further information on social back ground was obtained in respect f the mother employment. The mothers were employed in 51 families (35.2%) of the diabetic series and in 44 (34.9 %) of the non-diabetic. Full-time employment was met with in 21 (14.5 %) of diabetic mothers and in 21 (16.7%) of "non-diabetic the remainder being employed part-time Total correspondence was found in 71 of the pairs while in the remainder the diabetic mother worked in 22 and the "non-diabetic mother in 26 pairs.

Children under med cal supervision

At the beginning of the study in September 1960, 63 cases (43.4) 30 ♂ (52.6) and 24 ♀ (30 8%)—were under medical supervision at the diabetes clinic f Crown Princess Lovisa Children Hospital (KLB). The principles of treatment practised t this hospital have been reported previously (16, 17). The children not under treatment here were under the supervision of the other three children hospitals in Stockholm (Karolinska Sjukhuset, Samariten, Sachs) or of two general practitioners. Although opinions as to treatment may have differed among the physicians treating these children it was impossible further t divide this group not under KLB supervision and it will hereafter be referred to as KSSS children. All cases were classified into three grades f diabetic control, excellent" fair" or "poor" (25). In the KLB group 11 1% (1 ♂ 6 ♀) were classified as of "poor" control and in the KSSS group 71 6% (19 ♂ 39 ♀). Mean age at onset for all diabetics was 7 0 years (2 months to 17 years) and mean duration 5.9 years (8 months to 17 years).

Exam nations and nterviews

The diabetic and non-diabetic groups were observed during the school year 1960–1961 During this period the uthor had the opportunity f studying the behaviour f the children –5 times, occasions on which various examinations were made. Some f these were only for blood sampling, but the investigation of physical work capacity (26), the physical examination and dietary interviews gave the opportunity f at least one hour observation f the children mental reactions. During all these examinations and while the children were awaiting their turn as much information as possible was collected from each child. Furthermore telephone conversations (cf. 27) were held both with the parents and with the children. Several cases as ften diabetic as non diabetic, also pplied separately to the author for mental problems one or more times at their own or parents request All the above observations were used when assessing the mental status f the children, no attention being paid to the case histories

examination appeared relaxed, were easily approached and had a normal emotional tone were designated mentally undisturbed (cf 21).

All examinations and interviews took place at KLB. The interviews, made during a six week period in May–June 1961 lasted at least 30 minutes each, and even those mothers who were known from previous visits to KLB were seen. Since it was the mothers who answered the questions in all cases but 4 there was an opportunity of studying the mental health of the mothers at the time of the investigation. Information on siblings, parent and grandparents was recorded and regarded as family history this information including present age or age at death and cause of death as well as mental illnesses and symptoms of such a degree of severity that either hospital care or prolonged medical treatment had been required. The case histories were mainly drawn up according t a questionnaire elaborated by Nylander (1). Almost all the questions in it could be answered with a simple "yes" or "no" The recorded mental symptoms of the children were thus obtained t the interview with the mothers. As in Nylander s study it was stipulated that the symptom in question should have had a certain intensity and duration i.e. that it should have constituted a problem for the child or the members of the family and have been present at least during the time of the investigation, viz. 6 months. For the whole of the diabetic group and, where necessary for non-diabetics as well, in and out-patient records were studied and for those diabetics who were treated by private practitioners the doctor in charge of the child was approached in person for information. The case histories given by the mothers greed closely with the children s hospital records.

Intellectual capacity

In an unselected group of 26 matched pairs (12 ♂ 14 ♀) the child's teacher was questioned as to whether the child was atypical in its general behaviour or had shown noticeable mental symptoms during the past term. As an assessment of intellectual capacity the total marks (grades 1 3) gained in all subjects except singing, physical training, handicraft and drawing were recorded.

Statistical analyses were made according to current principles.

Results

In only a few cases did the mothers report any relevant complications of pregnancy There seemed to be no difference between the two groups, but maternity case records were not studied and the data have not been subjected to further analysis. Data on delivery and the birth weight of the children were available in 108 pairs. As shown in Table 3 there was obvious correspondence between the two groups. No further division of the material was made as the groups were similar even as regards number of firstborns and social group distribution.

Familiary mental disturbance

The family history of mental disturbance among relatives (one or more) recorded in numbers of children concerned is given in Table 4. Complete information could not be obtained in cases where the child or either of the parents were adopted or came from incomplete homes. The frequency of mentally disturbed relatives was somewhat higher throughout in the diabetic group.

On the basis of observations made at the interviews 40 mothers in the diabetic group (27 8 %) and 14 in the non-diabetic (11 1 %) were diagnosed by the author as mentally disturbed The difference was highly significant ($p < 0.001$) in the whole series and in matched pairs significant ($p < 0.01$ 33 against 13). Nine diabetic and 'non-

TABLE 3 *Birth weight (kg) and complications of delivery in 103 pairs (104 ♂ 11 ♀)*

	Diabetics			Non-diabetics		
	Boys	Girls n	Total n	Boys n	Girls n	Total
Birth weight < 2.50 kg	1	4	5	—	3	3
Birth weight 2.51 – 4.00 kg	39	47	86	41	48	89
Birth weight > 4.01 kg	12	5	17	11	5	16
Mean birth weight	(3.57 kg)	(3.44 kg)	(3.50 kg)	(3.64 kg)	(3.38 kg)	(3.50 kg)
Caesarean section	1	—	1	1	—	1
Forceps	4	—	4	1	3	4

diabetic mothers were diagnosed as mentally disturbed although no symptoms were reported in their case histories. The most common disturbance among the mothers was the occurrence of various symptoms of anxiety. Within this group 16 "diabetic" and 8 "non-diabetic" mothers were diagnosed as having anxiety neurosis, all but two belonging to matched pairs ($p < 0.1$). No relationship between broken homes and anxiety neurosis was found.

Mental symptoms

Mental symptoms in relation to sex and age are set out in Table 5. The frequency of cases without symptoms was the same in the diabetic group (54.5 %) as in the non-diabetic (55.6 %), in both groups higher for boys than for girls. The number of symptoms per case was numerically higher among the diabetics. Anxiety was the only symptom met with more often in the non-diabetic group.

A comparison was made within the matched pairs as to the frequency of appearance of symptoms if at least 8 children had the symptom in question (Table 6). Nine of 11 symptoms were met with more often among the diabetics ($p < 0.05$). Significant differences were found as regards two symptoms, namely emotional lability ($p < 0.001$) and difficulties with companions ($p < 0.05$), the diabetics displaying the higher frequency.

The frequency of symptoms was numer

TABLE 4. *Family history of mental health among relatives*

Figures indicate number of subjects in which mental disturbances was recorded among one or more relatives, and the figures in brackets the number of subjects where complete information was available

	Diabetics					Non-diabetics				
	Boys	Girls	Total			Boys	Girls	Total		
	n		n				n	n	%	
Grandparents	5	10	15	11.3	(133)	0	9	9	7.8	(116)
Fathers	11	12	23	17.3	(133)	6	9	15	12.7	(118)
Mothers	16	18	34	25.0	(136)	7	1	19	15.6	(122)
Siblings	2	9	11	7.6	(145)		3	5	4.0	(126)

TABLE 5 *The mothers' reports of mental symptoms in relation to sex and age*

D = Diabetics, N = Non diabetics.

	Age groups of diabetics												Age groups of non diabetics												Boys and Girls	
	7–10 ♂	7–10 ♀	11–12 ♂	11–12 ♀	13–14 ♂	13–14 ♀	15–16 ♂	15–16 ♀	17–20 ♂	17–20 ♀	Total ♂	Total ♀	7–10 ♂	7–10 ♀	11–12 ♂	11–12 ♀	13–14 ♂	13–14 ♀	15–16 ♂	15–16 ♀	17–20 ♂	17–20 ♀	Total ♂	Total ♀	D	N
No. of cases with symptoms	5	8	4	5	4	9	4	15	4	8	21	45	7	5	5	7	7	0	3	10	3	4	31	35	64	66
No. of cases without symptoms	15	10	7	7	14	7	7	0	6	3	46	33	8	8	8	5	9	5	5	9	9	4	39	31	79	70
Tics	1										1														1	0
Headache			1	3		3	1	3	2	1	4	8			1	1		1		4	1		2	6	13	8
Abdominal pain		3	1	1	1	1	2	2	3	1	6	9	1	2		4	1	2	1	3		1	3	11	16	14
Heart symptoms										1		1						1						1	1	1
"Growing pains"	1	1									1	3								1				1	4	1
Tiredness				9				4	3	3	3	8			1					6		1	1	7	11	8
Enuresis	1	1							1		3	1									1		3	5	2	5
Speech disorder					1						1						1						1		1	1
Motor restlessness	1					1	2				5	1								1				1	4	1
Nausea							1			1	1	1													2	0
Anorexia		1	1		1	1		1		1	3	4		1	1	1				1		1	1	4	6	5
Disorder of sleep		2			2	1	1		1	2	6	5	2						1	3			3	3	11	6
Emotional lability	3	6	1		3	7	2	7		1	8	26		1		2	2	3		3	1	1	3	9	34	1
Difficulties in concentration	1		1		1	1		3	1	1	4	4	2	1	2		2		1	1			7	2	8	9
Anxiety	1	1	1		1	2	1	2	1	2	5	7	4	3		3	4	4	1	2		1	9	12	12	21
Obsession-compulsion symptoms						1		3				2				1						1		2	3	2
Depression				1	2	3		1	1	3	2	7				1			1				1	3	10	4
Hysterical symptoms		1				1	1	1			1	3						1				1		2	4	2
Aggression	4	2			1	3	1			2	6	9					3	2		1		1	3	4	15	7
Difficulties with companions	3	1	1	1	2	5	2	6	1	4	8	17	1	2	1	2	1	1			1		4	8	25	13
Unsociability						3	1			1	1	3					2			1			2	1	4	3
No. of symptoms per case*	1.0	1.1	0.8	0.8	0.8	2.0	1.4	1.6	1.3	2.4	1.0	1.0	0.8	0.8	0.0	1.3	1.0	1.1	0.6	1.6	0.4	1.0	0.7	1.3	1.3	1.0
Total no. of cases	17	18	11	12	18	16	11	21	10	11	67	78	15	12	10	13	16	14	8	19	11	8	60	66	143	136

* Counted on total number of cases in the group.

TABLE 6 *The occurrence of most frequent mental symptoms in 77 matched pairs (53♂ 96♀) in which the diabetic (D) the non-diabetic (N) or both presented the symptom in question*

Figures denote number of pairs.

Symptoms	Symptoms in both D and N	Symptoms D only	Symptoms N only	Difference D–N
Headache	2	10	7	+ 3
Abdominal pain	—	12	13	− 1
Tiredness	1	11		+ 4
Anorexia	—	7	5	+ 2
Disorders of sleep	—	11	6	+ 5
Emotional lability	2	30	9	+21
Difficulties in concentration	2	6	4	+ 2
Anxiety	1	11	20	− 9
Depression	—	9	4	+ 5
Aggression	1	14	6	+ 8
Difficulties with companions		21	10	+11

ically higher among girls than among boys in both groups (Table 5) In the 17–20-year-old non-diabetics the frequency of cases with symptoms was low as opposed to that observed among diabetics. The highest number of symptoms per case in the diabetic group was found among boys aged 15–16 and girls aged 17–20 years the corresponding figures for non-diabetics being low

Certain differences were noticed as regards individual symptoms. Thus in both the diabetic and non-diabetic group headache and abdominal pain were found more often among girls than among boys. The frequency of emotional lability among diabetic girls was 33.3% and among diabetic boys 11.9% ($p < 0.01$). Difficulty with companions was also met with more often among diabetic girls (21.8) than among the boys (11.9) although the difference was insignificant ($p < 0.$) The frequency of individual symptoms was usually too low to allow assessment in relation to age It may be observed, however that emotional lability and difficult with companions were similarly found on the whole in all age groups.

Mental status

Mental status in relation to sex and age is given in Table 7 The frequency of mentally disturbed subjects is the same in both groups. No significant sex difference was apparent, and in the diabetic group the frequency was on the whole the same in the various age groups. Among the non-diabetics mentally disturbed cases were somewhat more common in the youngest age group Subjects recorded on examination as mentally disturbed showed great variation of symptoms both as to type and intensity Most cases had only mild mental symptoms, but 5 diabetics (1♂ 4♀) and 1 non-diabetic girl were so tense anxious and disturbed that they had to be designated as mentally insufficient. Seven diabetics and 8 non-diabetics were diagnosed as mentally disturbed in spite of the fact that their case histories were completely negative

A further assessment of the mental state

TABLE 7 *Frequency of mentally disturbed subjects (mental status) in relation to sex and age.*

Figures in brackets denote total number of subjects.

Age group	Diabetics Boys n	Girls n	Total n	%		Non-diabetics Boys n	Girls n	Total n	%	
7–10	3	6	9	25.7	(35)	6	3	9	32.1	(28)
11–12	1	3	4	17.4	(23)	3	2	5	22.7	(22)
13–14	2	3	5	14.7	(34)	3	5	8	26.7	(30)
15–16	3	6	9	28.1	(32)	1	5	6	22.2	(27)
17–20	2	3	5	23.8	(21)	—	1	1	5.3	(19)
Total	11	21	32	22.1	(145)	13	16	29	23.0	(126)

of some of the children was obtained from the opinion of the teacher Seven diabetics (4♂ 3♀) and 4 non-diabetics (3♂ 1♀) of various ages were described as mentally deviating from their schoolmates. All seven diabetics were said to have difficulties with companions while the four non diabetics showed other kinds of abnormality In all cases but one these subjects were reported by their mothers as having mental symptoms or were mentally disturbed on examination.

School reports

One diabetic boy was in a special class for retarded children, two were in a so-called "reading class while the remainder were in normal classes. In 7 matched pairs who remained classmates during the year of study the school reports were compared (Table 8) The great difference between the lowest and highest total marks is explained by the varying number of school subjects taught at different levels. No age or sex differences were observed and the means of total marks were almost the same in all groups for both autumn and spring term. During the spring term of 1961 the mean intra pair difference was 0.13 ± 0.40 being insignificantly lower in the diabetic group ($p < 0.8$) No connection was observed between school achievements

TABLE 8 *Distribution of total marks for the spring term 1961 in 72 (74♂ 70♀) matched pairs*

Total marks for spring term 1961	Diabetics Boys n	Girls n	Total n	%	Non-diabetics Boys n	Girls n	Total n	%
< 5	3	—	3	4.2	1	2	3	4.2
6–10	12	7	19	26.4	1	10	22	30.6
11–15	12	18	30	41.7	13	10	23	31.9
16–20	7	8	15	20.8	8	10	18	25.0
> 21	3	2	5	6.9	3	3	6	8.3
			72	100.0			72	100.0

TABLE 9 *Comparison between diabetics with and without pathological mental findings.* Figures in brackets denote number of cases.

	Pathological findings				No findings			
	Boys (8)	Girls (17)	Total (25)		Boys (43)	Girls (30)	Total (73)	
Mean age	12.5	13.4	13.1		12.6	12.5	12.6	
Mean age at onset of diabetes	7.0	7.9	7.6		6.5	7.4	6.9	
Mean duration of diabetes	5.5	5.5	5.5		6.1	5.1	5.7	
	n	n	n	%	n	n	n	%
Medical supervision at KLB	6	9	15	60.0	24	8	32	43.8
Poor diabetic control*	3	10	13	54.2	9	13	22	31.0
Mother mentally disturbed	4	7	11	44.0	7	2	9	12.3
Broken home	—		2	8.0	6	4	10	13.7
Overcrowding	2		9	36.0	12	10	22	30.1
Only child	1	4	5	20.0	5	6	11	15.1
Mother employed	3	5	8	32.0	11	13	24	32.9
Social group III	5	8	13	52.0	14	9	23	31.5

* In 3 cases the degree of diabetic control could not be evaluated.

and age at onset, duration or degree of diabetic control.

The diabetics

The diabetic series was further analyzed. Seventy-three subjects of normal mental status who were reported as not having shown any mental symptoms were compared with the 25 cases which had both pathological status and were reported as having various kinds of mental symptoms (Table 9) In two respects significant differences in frequency were found. The children with pathological findings had an increased frequency of mentally disturbed mothers ($p < 0.001$) and were also more often of "poor" diabetic control ($p < 0.05$)

The distribution of the 16 mothers from KLB and KSSS with anxiety neurosis was 5_9 % (9 cases) and 47.1 (7 cases) respectively When taking the proportion of cases at KLB into account, the expected frequency for KLB should have been 4 .8 %, but the frequency observed was not statistically divergent.

Out of the 119 diabetics of the matched pairs 15 children had mothers diagnosed as anxiety neurotic—8 of these children were reported to be emotionally labile. The corresponding figure for the remaining 104 diabetics was 22 ($p < 0.01$)

Of the 7 KLB diabetics who were grouped under "poor" control 5 had mental symptoms, 5 showed mental disturbance on examination, * came from homes where there had been divorce and in 4 cases the mothers were mentally insufficient. The distribution in the various hospitals of the most frequent individual mental symptoms, emotional lability was calculated for girls. Nine cases of 26 (34.6 %) belonged to KLB this being quit comparable with the expected 33.3 Fifteen of 17 (88_%) with emotional lability at KSSS were grouped as being of poor" control—the expected figure was 76.5 %.

Discussion

When analyzing factors which influence mental health, the complicated circumstances xisting mak it difficult to arrive

at any definite causal connection. In order to come to any conclusions of general validity for the young diabetic population it was considered necessary to examine a matched control material. Due to other lengthy investigations on the same material it was necessary to deal with co-operative subjects, and so endeavours to obtain 100 % participation were not made. Rejected elements were as expected more badly situated in a number of respects than those selected, this being especially pronounced for the non-diabetics. A further explanation of the discrepancy between the groups is the one year lapse between the matching and the commencement of the study. During this time divorces were granted in a further 3 diabetic families. The occurrence of broken homes in 15 % of the diabetic group was higher than in the non-diabetic but owing to the form of selection no comparison was justifiable. The frequency seems to tally with the common experience in Stockholm whereby broken homes have been reported in 12 %—unpublished observations cited by 21—and 21 % (10) of all families. However, the goal set up was attained and the groups were essentially comparable even in other respects, e.g. delivery and early postnatal development.

The frequency of mentally disturbed mothers was significantly higher in the diabetic than in the non-diabetic group. The difference could largely be attributed to the increased number of neurotic mothers who had anxiety as the dominating symptom. This type of insufficiency is probably the most likely kind of reaction in mothers with a diabetic child. No connection between broken homes and mothers diagnosed as having anxiety neurosis could be established, and so the unbalanced distribution of broken homes observed would seem to have no primary importance.

In spite of this somewhat more unfavourable family situation among the diabetics, the groups had the same frequency of symptom free subjects both on examination and as reported by the mothers. When disturbed, however, the diabetic children seemed to be more seriously influenced—they had more mental symptoms per case and more diabetic subjects had to be classified as mentally insufficient on examination. In a previous KLB study on juvenile diabetics with at least 15 years duration, pathological EEGs were found in 31 % (11). Even if this observation might speak in favour of the hypothesis that diabetic children should show psychical signs of brain damage syndrome (3), the case histories (25, 27), the uncomplicated deliveries (Table 2) and the mental symptomatology (Table 5) in the present study do not support this view. When judging the children's mental status there was no evidence of a uniform psychological picture in the diabetics, a characteristic "diabetic personality" (19).

The diabetics had a numerically higher incidence of most mental symptoms, but comparison within the matched pairs was not entirely in favour of the non-diabetics. Thus two symptoms including anxiety of eleven were met with less often in the diabetic group. Certainly it is not advisable if at all possible to rely too much on one or two symptoms in a series of more or less subjective estimations. It is also impossible to say, for example, whether emotional lability in a diabetic child might have

the same meaning as anxiety in a comparable non-diabetic. The description of the symptomatology and the symptomatology itself of a disturbed child is probably highly influenced by the mother's state of mental health. Speaking in favour of this contention is the higher frequency of emotional lability in the children of mothers with anxiety neurosis than among the remainder of the matched diabetics. Emotional lability must also be considered to be directly connected with the day-to-day manifestations of diabetes. Fluctuations in blood sugar level leading to frequent insulin reactions might just as well have been reported as emotional lability. Since the higher frequency of emotional lability among diabetics was significant the two possible causes may well have had an additive effect.

The mothers of diabetics reported their children as having difficulties with companions more often than the mothers of non-diabetics. This finding was supported by the opinion of the teacher and may fit in with the low physical work capacity and the declining frequency of participation in physical training by the diabetics of this material (20). It is of interest to note that in a sociometric study on another handicapped group, overweight children, Börjeson (7) found the classmates rating of the overweight children to be mainly the same as in the controls. However, highly overweight boys with low physical work capacity received a significantly lower score when the choice concerned physical activity. Such experiences may give rise to adjustment problems influencing the future life and social adaption of the diabetic as well as the overweight child. In consistency with this suggestion there was a tendency with advancing age in the diabetic group towards an increase in cases with symptoms and an increase in mental symptoms per case. The reverse situation was found among the non-diabetics. The most pronounced shift was after puberty and diabetic girls were the most unfavourably situated, as also observed by others (5).

Among the many factors related to mental health in children one could be demonstrated statistically to influence the nervous symptoms of the diabetics, namely the state of mental health of the mothers. Similar observations are common in child psychiatry (12).

As the type of medical supervision greatly affects the control of diabetes, it was impossible to analyze thoroughly the relation between environmental and psychological factors on the degree of diabetic control. The findings in a small group of cases classified as of "poor" control suggest, however, that an unfavourable family situation and mental symptoms in the child were often connected with "poor" diabetic control. Diabetic girls with emotional lability also had an unexpected high frequency of "poor" control, and the diabetic group with pathological mental findings had an increased frequency of "poor" control as compared with those without mental findings. Thus an interrelation between mental disturbance and degree of diabetic control might possibly have been demonstrated.

The intellectual capacity of diabetic children has been much discussed and the literature recently reviewed (1). No significant differences in school achievement could be demonstrated between the two groups and the frequency of diabetic cases

in special classes tallies with that generally met with in Stockholm. Thus the IQs of the diabetics might be regarded as falling within normal limits. This finding agrees with earlier studies on non-selected materials (6 9) An early age of onset of diabetes (1) has been claimed to exert an unfavourable influence on the intellectual capacity of the diabetics, but the present findings and those of others (14) do not support such an opinion.

There seem to be no investigations on diabetic children and adolescents which can be directly compared with this study In the few instances where large series have been assembled the investigations were chiefly built up around a battery of psychological tests alone, no clinical study being made nor the state of mental health of the parents being assessed The present observation of roughly the same frequency of disturbances in behaviour among diabetic children as among controls has, however been made by others (6 8 14)

The findings of this study support Danowski (9) who states that "the diabetic child is not doomed to personality disturbances as an intrinsic manifestation of his metabolic disturbance It may be of psychiatric interest that not even such a serious somatic disorder as diabetes mellitus necessarily causes emotional problems. When investigating psychological symptoms in a consultation material, Nylander (22) in agreement with this statement, found in a group of children with definite somatic disease that 49 % had no mental symptoms but that in a comparable group without somatic disorder but with psychosomatic symptoms only 7 % were free from mental symptoms.

It has been suggested that no chronic disease of childhood produces more anxiety in a mother than diabetes mellitus (4) Virtually all parents of physically handicapped children have a feeling of guilt and of personal responsibility for the handicap (13) Thus even in a study of children operated upon for congenital heart disease it was found that environmental factors, particularly the mothers attitude seemed to be almost equally important causes of the post-operative improvement in the behaviour of the children as the surgical cure or the alleviation itself (15)

Clinical experience has taught that the onset of diabetes mellitus imposes greatly on the personalities of the parents themselves and on their attitude to the child. It is not known why how often or to what extent the children and the parents become seriously disturbed, but these questions are the subject of a study now in progress at KLB (2) As pointed out by Stearns (24), parents of diabetic children may need to be helped with their own problems before they can become a source of support for the child (28) One of the arguments in favour of a free diet for children with diabetes mellitus was a reference to the psychological injuries which would probably manifest themselves if strict therapeutic principles were applied (18) The present diabetic material was composed of two almost equally large divisions as regards the type of treatment involved. When comparing the two groups in respect of the frequency of mothers with anxiety neurosis and the frequency of emotional lability among the children, no statistical differences were obtained. It therefore seems justifiable to conclude that the possibly heavier stress on the

strictly treated diabetic group was counterbalanced by other factors, probably referable to the greater time spent on instruction (16). It has been said (12) that the fight against such a hidden enemy as diabetes is a greater burden for a child than to have a visible handicap. In order to avoid anxiety reactions in the children as well as the parents and still to keep up a good control of the diabetic state known facts about the disorder and the ways of managing it must be taught both carefully and repeatedly.

Summary

In a material of 145 diabetic and 126 matched non-diabetic schoolchildren aged 7–20 years, the social and family structure was investigated. Family history of mental disturbances and actual mental symptoms of the children were obtained by interviews with the mothers. A diagnosis of the mental health of the children and their mothers was arrived at by clinical judgement. Roughly half the diabetic series was treated more strictly and intensely than the other.

The diabetic group had a significantly increased frequency of mentally disturbed mothers who mostly displayed various anxiety symptoms.

The frequency of children without reported mental symptoms was the same in the two groups. On examination mentally undisturbed cases were found as often in the diabetic as in the non-diabetic group. The diabetics, especially the older ones, showed somewhat more symptoms per case. The most common symptoms among the diabetics were emotional lability and difficulties with companions.

School achievements were evenly performed by the two groups and uninfluenced by the age at onset of diabetes.

Diabetic children with pathological mental findings had a significantly increased frequency of mentally disturbed mothers. Cases of "poor" diabetic control were found to have mental symptoms more often than those of "fair" control. In the strictly treated diabetic group there was no increase in problems of adjustment neither as regards the mothers nor the children.

In order to avoid anxiety reactions, the need of careful instruction of both parents and children is emphasized.

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Niemann Pick Disease in Infancy

Report of Two Siblings with Clinical Histologic and Chemical Studies

by BIÖRN I IVEMARK, LARS SVENNERHOLM, CLAES THORÉN and RAGNAR TUNELL

Niemann Pick disease is generally characterized as a familial metabolic defect with storage of sphingomyelin in the visceral organs and the central nervous system [2 7 16]. Two siblings with this disorder have been encountered recently in Stockholm—the second and third cases to be reported in Sweden, the pathologic features of the first was discussed by Henschen in 1925 [14]

Case Reports

Family history

The two siblings were the only children of consanguinous marriage As may be seen from Fig 1 the parents were half-first cousins with a common grandfather who lived healthy throughout his 83 years. The family history has been traced back to the sixteenth century when the family appears to have emigrated from England. There was no Jewish blood. Only one other consanguinous marriage is known in the family but no other cases of lipidosis. The family is not limited to any geographical, social or religious isolat

The father had mild infectious hepatitis in 1935. Liver function test performed in 1960 were normal. During the same year when 36, the father had an acute myocardial infarction. Coronary angiograms indicated coronary sclerosis. The blood lipid analyses showed high values with cholesterol 27° and total lipids 1100 mg%. The values for phospholipids, lecithin, sphingomyeline and triglycerides were within normal limits.

The mother had always been healthy. Her liver function, examined by routine laboratory tests, was normal and serum lipid determinations showed a slightly elevated cholesterol value (266 mg%) but the other lipids were within normal limits. Examination of the parents bone marrow in 1962 disclosed normal pictures. Lymphocytes and monocytes in peripheral blood from the parents amounted to 51 and 5% for the father and 50 and 2% for the mother. Of 100 mononuclear cells counted, the numbers definitely vacuolized cells were 5 and 2% respectively

Clinical findings

Case 1

The parent first child, a boy was born at term 1956. Pregnancy labor and delivery were normal. Birth weight 3120 g

Blood films and bone marrow were kindly evaluated by Dr P O. Hallberg at the Kronprinsessan Lovisas Barnsjukhus.

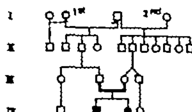


Fig. 1 Pedigree of family The two cases of Niemann Pick disease occur in the fourth generation. The parents are half-first cousins.

The immediate neonatal period was uneventful except for the presence of jaundice on the second day of life This reached a maximum on the fourth day but throughout the course of the disease it never disappeared completely The condition was associated with yellowish-brown urine and light stools.

Course —There was swelling of the abdomen and the weight remained low During the subsequent 3 months the clinical findings were grossly unchanged. The boy was poorly nourished, weighing 3510 g at 6 weeks and 3640 g at 3 months; he was moderately icteric had normal reflexes and psychomotoric development. The liver and spleen were enlarged and extended 5 and 6 cm beneath the costal margins, respectively

The child was thought to have obstructive jaundice and at the age of 9 weeks he was referred to Kronprinsessan Lovisas Barnsjukhus. An exploratory laparatomy and a biopsy of the liver were performed and at the time the findings were thought to be compatible with cirrhosis secondary t "neonatal hepatitis"

During the fifth month of life the jaundice became more severe the child general condition remained poor during the last 10 days of life he increased 600 g in weight owing primarily to edema and ascites. He died suddenly at 5 months of age

Case 2

The parents second child, a girl, was born at term in 1960 Pregnancy labor and delivery were normal. Birth weight 3970 g

The immediat neonatal period wa uncomplicated. Persistent jaundice was noted on the second day of life and at 49 days of age the child was admitted to the Pediatric Clinic of the Karolinska sjukhuset.

Course —The child was malnourished and weighed at 12 weeks 3850 g. There was moderate jaundice but the child was active and psychomotor development reflexes and body posture were normal. The abdomen was distended and the liver and spleen were enlarged, both of them reaching 7 cm below the costal margin.

No complete biliary tract obstruction was present. Examination of duodenal secretion after administration of cholecystokinin revealed bile acids and pigment. A needle biopsy was performed at three months of age and the changes were considered compatible with neonatal hepatitis" and cirrhosis.

At 5 months of age the clinical picture was changed. The jaundice gradually increased, and the child lay continuously in the opisthotonus posture with slight hyp tonicity of the arms and legs; there was constant convergent strabismus. She became less active but still showed interest in her surroundings. The spleen increased rapidly in size and at 6 months of age completely filled the left side of the abdomen (Fig 3). No abnormal pigmentation of the retina was found. EEG examination showed a normal pattern.

Steroid therapy was instituted at 6 weeks with 6 mg prednisolone/day without effect and treatment was discontinued after one month. One transfusion of 100 ml blood given at 6 months resulted in a marked but short improvement. At 8 months of age the child developed edema and ascites and she died suddenly

Laboratory findings

In both cases liver function tests with total and direct bilirubin, thymol flocculation tests, GOT and GPT determinations were repeatedly performed during the course of the illness (Fig 2) The bilirubin values in particular indicate unchanged liver function during the first months. Later the liver function tests indicated rapidl progressive liver cell damage. Repeated electrophoresis examinations showed only gamma globulin frac

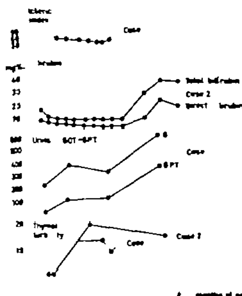


Fig. _. Some of the liver function tests performed from 1 month of age until death t 5 months in Case 1 and t 6 months of age in Case _. The similarity in the course of the disease up t 3 months in the two cases is brought out well in these curves.



Fig. 3. Case at 7 months of age. The spleen at this time almost filled the left half of the b-domen. The liver was also enlarged. The general status was extremely poor

tions consistently levated t 20% of the total protein, which ranged from 6.5 to 8 g. ESR *0–40 mm/1 hr. Progressive anemia, leucopenia and thrombocytopenia appeared eventually. The values in Case 2 ere as follows hemoglobin 12.6–7._ g. hit cells 10,800–2900 and platelet 500,000 –60,000 per mm at 2 and 6 months of age. Whit cells in the peripheral blood of Case 2 included 52% lymphocytes and 16% monocytes of these about one-half and one-third, respectively were acuolized to some degree. I the blood films there were no Niemann-Pick cells.

There wa a progressiv tendency for bleeding from the gastro-intestinal tract in Case 1 and with epistaxis in Case _. The prothrombin index was slightly depressed in both cases throughout the disease with alues between 60 and 0 of normal. Coagulation and bleeding times were normal lthough there was a slight thrombocytopenia. There was no iso-immunization in either case.

The bone marrow in Case 2 t 7 months contained large foam cells—classical Niemann Pick cells—which constituted bout 1 of the total count. They varied in size between *0 and 60–80 microns. All of them were PAS negative. The nuclei were usually displaced to the periphery and the cytoplasm contained numerous vacuoles of varying size. The skeleton showed demineralization but no

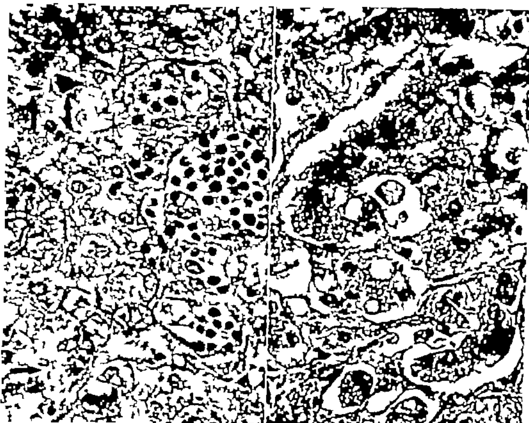


Fig 4. Fig 5

Fig 4 Case 1 Liver biopsy at the age of 9 weeks. A moderate distortion of lobular architecture. The parenchymal cells are large and vacuolized. An area of hematopoiesis is seen on the *right*. *Vertical arrows* point to bile casts in canaliculi; a PAS-positive Niemann Pick cell is seen lining a sinusoid (*horizontal arrow*) PAS. 465.

Fig 5 Case 1 Liver at autopsy at the age of 5 months. Distortion is more marked and the intercellular reticulum is increased. A Niemann Pick cell is seen in the center (*arrow*). H & E. 465.

destruction of the long bones. X ray findings for the chest were normal

In Case 2 blood lipid examination at 7 months of age revealed low lipid values with total lipids 430, cholesterol 88, phospholipids 170, sphingomyelin 24 and triglycerides 120 mg%.

Pathologic findings

Case 1

Paraffin blocks from formalin fixed liver biopsy and the autopsy specimens were available for study. The staining methods used were: hematoxylin and eosin, Verhoeff van Gieson, PAS, toluidin blue before and after sulphation with fuming sulphuric acid -acetic anhydride-ether mixture [17], Mallory's phosphotungstic acid-hematoxylin and the Prussian blue reaction for iron. No material was available for fat stains

The *biopsy specimen* taken from the liver at 9 weeks disclosed a slightly distorted lobular pattern (Fig 4). The connective tissue in the portal tracts was slightly increased as was the intercellular reticulum. There were occasional islands of hemato-

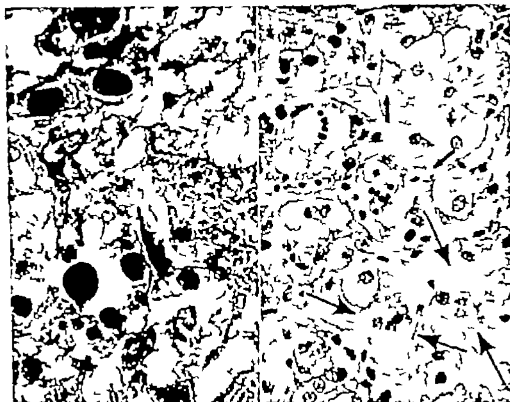


Fig. 6. Fig. 7

Fig. 6. Case 1. Liver at autopsy showing hyaline bodies and Niemann-Pick cell (arrow). 465.

Fig. 7. Case 2. Liver biopsy at the age of 3½ months showing swollen parenchymal cells, and, between large arrows, giant-cell transformation. The giant-cell on the right contains bile pigment. Small arrows indicate PAS positive Niemann-Pick cells. PAS. 465.

poiesis in the sinusoids. A moderate number of bile casts were present in the canaliculi. The parenchymal cells were greatly swollen and contained vacuoles. In the sinusoidal walls and the periportal connective tissue there were scattered large PAS-positive cells. These contained abundant granular cytoplasm, which was metachromatic after but not before sulphation. There was no giant-cell reaction or evidence of inflammation, and no pigmented cells were found other than the bile-stained parenchymal cells. The Prussian blue reaction for iron was negative and no acidophilic bodies were encountered.

Autopsy. The body measured 54 cm and weighed 4960 g and showed a greatly distended abdomen containing 700 ml of a slightly blood tinged ascitic fluid. The *liver* was enlarged (weight after fixation 330 g; normal 188 g), firm and brownish yellow; the capsular surface was slightly puckered. The porta hepatis contained a moderately enlarged *lymph node* which did not compress the normal extrahepatic bile ducts. The *spleen* was enormously enlarged (weight after fixation 175 g; normal 16 g), firm and brownish-red. In the *lungs* a few petechial hemorrhages were found. The remainder of the gross examination was essentially nega-

tive. No examination was made of the brain. Specimens for microscopic examination were taken from the liver spleen, pancreas, kidney and lymph node and fixed in formalin.

Microscopic examination of autopsy speci mens from the *liver* disclosed a more marked distortion of the lobular pattern (Fig 5) than had been noted in the biopsy specimen three months previously There was an increase of the periportal connective tissue and numerous bile casts were seen in the canaliculi. Many parenchymal cells showed vacuolization and a large number of granular PAS-positive diastase-resistant cells were present in the sinusoids. Those cells also showed metachromatic staining after sulpha tion In a few areas large numbers of acidophilic PAS-positive hyaline acidophil c bodies were present (Fig 6) There was no hematopoiesis. The sinusoids of the *spleen* were distended by numerous foam cells with the same staining characteristics as those in the liver The Malpighian bodies were atrophic. The *lymph nod* from the porta hepatis was almost completely transformed by foam cells, only very occasional collections of lymphocytes being found. This lymph node revealed no pigmented histiocytes In the *kidn y* several glomeruli con tained foam cells. The *pancreas* appeared normal.

The structural changes and the foam cells in the visceral organs are compatible with the diagnosis f N emann Pick disease

Case 2

The *needle biopsy* specimen taken at the age of 3½ months was f xed n Stieve solution and embedded in paraffin. The *l ver* showed a moderat distortion of the lobular pattern (Fig. 7). There were bile casts in canaliculi nd bile pigment in a few paren chymal giant cells. A few sinusoidal cells were swollen, and their cytoplasm was granular PAS-positive and metachromatic after sulphation. The histologic picture wa thought to be compatible with giant-cell hepatitis with early cirrhosis.

Autopsy wa performed 4 hours after death. The *lungs* were yellowish-red and moderately atelectatic. The *cardiovascular system* was normal. One thousand ml of clear straw-coloured fluid were found in the *peritoneal* cavity The *l ver* was slightly en larged (weight 290 g, normal 230 g) firm and greenish black in colour The wall of the portal vein was thickened. There was an enormous *spleen*, weighing 235 g (normal 20 g), firm, bluish-red peripherally and yellowish-brown at the center Several moderately enlarged brownish yellow *lymph nodes* were present in the retroperitoneal space porta hepatis and mediastinum. The *adrenals* were grossly normal, as were the pancreas, thyroid, ovaries and thymus, The *kidneys* appeared slightly enlarged, the left one contained few small cyst in the cortex and medulla. The urinary tract was normal. The brain was normal grossly

Microscopic examination disclosed changes in the brain, spinal cord, li er spleen, lymph nodes, thymus, bone marrow lungs and kidneys. The specimens were fixed in formalin, and in addition to the stains men tioned bove for Case 1 frozen section were prepared for Sudan III staining and PAS from the brain spinal cord, liver spleen, lymph nodes, bone marrow and kidneys. Fl orescence microscopy was performed on unstained specimens from lymph nodes, liver and spleen.

Cha ge n sceral organs.—Large numbers of typical Niemann Pick cells were present in lymph nodes, spleen, thymus lung, bone marrow and liver A moderate number of such cells were found in the glomerular tuft of the kidney (Fig 9). All these visceral foam cells showed a varying amount of PAS-positive cytoplasm, and t luidin blue metachromasia was evident after sulphation.

The *liver* specimens taken at utopsy revealed severe changes which more clearly disclosed the storage character of the process than the biopsy specimen taken 5 months earlier The alterations were similar to those found in the liver of Case 1 with marked disruption of the lobular and cell-cord pattern, trophic vacuolized parenchymal





Fig. 8. Fig. 9

Fig. 8 Case 2. Lymph node containing numerous Niemann-Pick cells. The littoral cells are converted t pigment laden large cells, containing lipo-pigment. PAS. 175

Fig. 9 Case 2. Kidney with Niemann-Pick cell in glomerulus. Toluidin blue after sulphation. 465.

cells, numerous bile cast and Niemann-Pick cells in the sinusoids. N acidophilic bodies and no iron deposit were present.

The *lymph nodes* were lmost complet ly composed of foam cells (Fig 8). In addition, the littoral cells of the sinuses contained coarse granules of yellowish-brown pigment, positive t Sudan Black B, negat ve t Sudan III and positive to PAS, which did not display metachromasia before or after sulphation. This pigment was utofluorescent in frozen sections but not in paraffin embedded specimens. The staining characteristics indicat that the pigment was probably ceroid [21 23]. Such pigmented cells were not found in any other organ.

Changes the central nervous system.— Several ganglion cells in the basal ganglia, pons, medulla oblongata, cerebellum and spinal cord showed ballooning of the cytoplasm typical of Niemann-Pick disease (Fig 10) The cytoplasm was finely granular slightly metachromatic after sulphation, but PAS-negative in all sections from paraffin blocks. Sections stained with phosphotungstic acid—hematoxylin showed slight bluish-brown precipitat in the cytoplasm. In frozen sections ballooned ganglion cells contained no sudanophilic material, but a fine dust of PAS-positive substance was observed (Fig 10) This had pparently been dissolved during the embedding procedure



Fig 10 Case 2. Brain. Nucleus ambiguous. *In the right half* ballooned ganglion cells with PAS-negative cytoplasm after embedding in paraffin. *In the left half* frozen section from the same area, showing PAS-positive granules in the ballooned ganglion cells. 445

and most probably represented gangliosides. None of the sections displayed changes in the cortical ganglion cells. Sections stained for myelin showed no evidence of demyelination but the myelination appeared to be less developed than is normal for the age.

Summary of pathologic findings—In both cases hepatomegaly and splenomegaly were *prominent* with a *more than* tenfold increase in the size of the spleen owing to the presence of numerous Niemann Pick cells. The livers also showed Niemann Pick cells, atrophy of the liver cell-cords and cholestasis. In both cases Niemann Pick cells were found in great numbers in lymph nodes, which in Case 2 also displayed a lipo-pigment of ceroid type. In addition Niemann Pick cells were present in the lungs and in the renal glomeruli. In Case 2 where the CNS was examined the ganglion cells displayed ballooning typical of Niemann Pick disease

Chemical investigation

A chemical examination of the organs was performed only in Case 2.

Method—Deep frozen specimens of the cerebrum, sciatic nerve, liver spleen, kidney and lymph nodes were analyzed. The handling of the material and the methods applied have been described elsewhere [27]. In addition, chromatography was performed on thin layer plates of silica gel to separate free and esterified cholesterol and for the identification of other lipids. The sphingomyelins were prepared from liver and spleen by hydrolyzing a total lipid extract with 1 N potassium hydroxide in water at 37 [1] The sphingolipids were separated by chromatography on silicic acid and alumina.

Results.—A *pronounced increase* in the relative and absolute amounts of sphingomyelins was found only in the spleen and the lymph nodes. The component of sphingomyelins were the same as from normals. The weight of the spleen was more than ten times that of normal infants of the same age and the content of sphingomyelins was about seven times as great. The absolut amount of sphingomyelins was thus about one hundred times the normal value A comparable increase in size and concentration of sphingomyelin was also seen in the lymph nodes; no

[1] This preparation was kindly performed by Dr E. Svennerholm

TABLE 1 *Lipid composition of extra-cerebral tissues*

The values are expressed as per cent of dry weight. In brackets the mean values for two normal infants, one and two months of age

	Spleen		Lymph node		Liver		Kidney		Sciatic nerve
Water*	78.7	(78.7)	86.4	(87.5)	77.5	(78.6)	83.5	(82.7)	—
Nitrogen	10.5	(13.8)	9.5	(12.7)	11.8	(11.8)	12.[illegible]	(1[illegible].4)	10.9
Total lipids	30.3	(8.8)	29.0	(8.9)	17.8	(12.6)	13.4	(10.0)	[illegible]7.1
Triglycerides	0.3	(0.8)	0.4	(—)	0.2	(—)	0.6	(0.6)	14.2
Cholesterol	10.4	(1.6)	9.4	(2.2)	3.3	(1.3)	[illegible].9	(1.4)	2.8
Phospholipids	18.7	(6.0)	18.1	(4.5)	11.4	(8.6)	6.2	(7.8)	7.1
Kephalins	[illegible]	(2.5)	6.8	(1.4)	5.0	(3.3)	2.0	(3.7)	2.7
Lecithins	8.1	(2.2)	3.8	(3.4)	3.9	(3.8)	3.1	([illegible].6)	2.8
Sphingomyelins	8.6	(1.1)	7.0	(0.9)	2.5	(0.8)	1.8	(1.1)	1.8
Homoglycolipids	0.9	(0.2)	—		0.57	(—)	1.4	(0.5)	3.2

* Percentage of the fresh weight.

quantitative figures can be given, however as the size of the lymph nodes can be evaluated only approximately. Compared with the large accumulation of sphingomyelins in the spleen and lymph nodes the increase in kidney and liver was small (two- to three-fold). There was also an increase in cholesterol and glycero-phospholipids (lecithins and kephalins) in the affected organs (Table 1). Only a small amount of the cholesterol was esterified (in spleen and lymph nodes about 5% of total cholesterol).

The findings for the assay of the brain tissue are of considerable interest. Whereas the lipid values were normal for the grey matter, for the white matter they were similar to those found at the age of about 2–3 months (Tables 2 and 3). The figure for sphingomyelins in the white matter is significantly lower than that of normal infants of the same age.

The concentration of gangliosides, evaluated by estimating lipid hexosamine, was about the same in cortical grey matter as in normal infants of the same age and slightly higher than normal in the white matter. This increase is not real, and can be accounted for by defective myelin formation, as the gangliosides are components of axons but not of the myelin sheaths. As the histologic examination revealed signs of increased ganglioside content of the basal ganglia, pons, medulla oblongata, cerebellum and spinal cord, specimens from these regions were analyzed. The results of the chemical analyses of grey matter from these areas show values between 0.18–0.10% for lipid hexosamine. The values are difficult to interpret, however, as in these areas grey and white matter are difficult to separate. The determinations are thus strongly influenced by the amount of myelin structures in the slices used for the assays. There was possibly a slight increase in gangliosides.

Discussion

Despite the close similarity—occasionally amounting to identity—between the two cases in respect of the clinical and histologic findings, the diagnosis of Niemann-Pick disease was not established until the histologic and chemical examinations of the second case were completed. In the first case the basis for a definite diagnosis is inadequate since no chemical analysis or examination of the central nervous system was performed at autopsy. However, the similarity to the sibling in respect of the clinical and structural

Table 2 *Lipid composition of cerebral grey matter (frontal lobe)*

The values are expressed as per cent of dry weight.

	Normals				Present case
	1 mo	2 mos.	1 yr	1.5 yrs.	(8.5 months)
Water*	—	87.72	87.8	87.24	[illegible]
Nitrogen	9.56	9.78	9.86	9.22	9.28
Hexosamine (total)	0.71	0.76	0.70	0.83	0.83
Total lipids	28.5	28.7	31.3	33.3	[illegible]7.4
Cholesterol	6.1	3.4	[illegible]	8.0	6.3
Phospholipids	21.9	22.9	[illegible]4.3	[illegible]4.0	[illegible]0.7
Kephalins	10.7	12.3	10.9	11.7	9.3
Lecithins	10.1	8.7	10.1	10.5	10.0
Sphingomyelins	[illegible]	1.6	2.2	1.9	1.4
Homoglycolipids (cerebrosides + sulphatides)	0.47	0.39	0.78	0.45	1.10
Heteroglycolipids Lipid hexosamine	0.16	0.19	0.18	0.18	0.20

* Percentage of the fresh weight.

findings points strongly to a diagnosis of Niemann Pick disease.

If this deduction is correct the trait would probably have been transmitted from a common great grandfather. This would support the concept of an autosomal recessive transmission in Niemann Pick disease [9 15 20 30]. The parents would then be heterozygous carriers of the defective gene. The fact that the father had coronary thrombosis with myocardial infarction when only 36 years of age is remarkable but might still be coincidental.

The fulminant clinical course wa

Table 3 *Lipid composition of cerebral white matter (frontal lobe)*

The values are expressed as per cent of dry weight

	Normals				Present case
	1 mo.	2 mos.	1 yr	1.5 yrs.	(8.5 months)
Water*	—	83.29	81.60	77.36	86.8
Nitrogen	9.04	[illegible]65	7.43	[illegible]	8.43
Hexosamine (total)	0.70	0.48	0.42	0.43	0.75
Total lipids	28.8	39.8	50.3	57.7	33.6
Cholesterol	7.8	8.4	12.4	16.6	8.3
Phospholipids	19.5	25.4	27.2	29.8	20.9
Kephalins	8.1	12.6	14.9	16.2	10.4
Lecithins	10.1	8.4	9.2	8.8	8.9
Sphingomyelins	1.4	[illegible]3	3.0	4.2	1.5
Homoglycolipids (cerebrosides + sulphatides)	1.4	6.0	10.7	10.9	8.4
Heteroglycolipids Lipid hexosamine	0.14	0.15	0.08	0.00	0.13

* Percentage of the fresh weight.

characterized by a predominantly visceral localization of the disease with hepatosplenomegaly and jaundice as the principal signs In this respect these two patients are similar to five of Crocker & Farber s [9] cases who had significant and prolonged jaundice in the early months of life The morphologic changes as well as the laboratory investigations indicate severe parenchymal liver damage, which though uncommon in classic Niemann Pick disease [20], is reminiscent of Case 8 in Crocker & Farber s study These authors discuss the possibility of early hepatitis which would account for a permanent metabolic derangement in the liver and hence a gradual development of the storage disease.

In both cases the early structural changes of the liver were giant-cell transformation, bile stasis and fibrosis. The occurrence of Niemann Pick cells in the liver during the early stage of the disease was not as prominent a feature as the other morphologic changes, which may be encountered in a variety of conditions such as erythroblastoma foetalis [5] giant-cell hepatitis [6, 13, 26] various forms of cirrhosis [22] and hemochromatosis [12 19].

The coincidental history of endemic hepatitis for the father at the time of birth of Case 1 would also justify the suspicion of infectious hepatitis. However the *mother did not display signs of hepatitis* and her liver function tests were normal. The structural changes in the livers, especially the presence of acidophilic bodies in the liver of Case 1 (Fig 6) would seem to support this diagnosis [31], but these bodies occur in a variety of conditions [4] Further it was impossible to find definite evidence of inflammation in the livers The most likely cause of the cholestasis was compression of the biliary canaliculi by Niemann Pick cells.

The other structural changes found in the livers may be looked upon as manifestations of the neonatal liver non specific reaction to injury Whatever the cause of the liver damage its severity would account for the fulminant course of the disease

The accumulation of lipo-pigment in the lymph nodes in Case is a fairly uncommon feature of Niemann-Pick disease although it has been found by previous observers in long-standing cases of lipidoses [7] The presence of lipo-pigment is considered to be secondary to the lipidosis which may well cause a rapid and widespread tissue damage accompanied by failure to metabolize polyunsaturated fatty acids. Thus it seems not to be a primary disorder as it is in pigmented histocytosis [18 21]

Bloom [3] demonstrated marked vacuolation in a considerable number of lymphocytes in Niemann Pick disease and Videbaeck [29] showed that about a quarter of the cases he reviewed had vacuolized mononuclear cells. The presence of vacuolated lymphocytes in lipidosis has been thoroughly studied by Rayner [25] There was no doubt of the presence of numerous vacuolized lymphocytes in Case 2 of the present communication. The findings of vacuolized mononuclear cells in peripheral blood from the parents is presumably an expression of heterozygosity as suggested by Rayner in lipidosis.

Severe mental retardation has been reported in almost all patients dying of Niemann-Pick disease [9]. In our Case 1

no definite mental or neurologic involvement was present at the time of death but in Case 2 neurologic abnormalities during the last months of life are fairly consistent with the microscopic findings of severe changes in the basal ganglia cerebellum medulla oblongata and spinal cord.

In the nervous system there was no increase in sphingomyelin, in fact in the cerebral white matter the sphingomyelin concentration was lower than in normals of the same age. Klenk [16] originally found the sphingomyelin content of the brain to be abnormally high in Niemann Pick disease and this has been confirmed by others [2, 11] On the other hand one case of a decrease in sphingomyelin in whole brain has been reported [28] Crocker & Farber [9] found the sphingomyelin content occasionally to be increased in the grey but not in the white matter

Crocker [8] has suggested that the discrepant result of the brain analyses in Niemann-Pick disease may be accounted for by the existence of different types of the disorder Only in the infantile "classic" type with serious neurologic impairment was a high level of brain sphingomyelins found It is possible that there are several genetically distinct forms of sphingomyelinosis, but such a hypothesis is not supported by the figures for sphingomyelins obtained with more or less specific methods by different researchers. Dawson [10] and Ansell & Spanner [1] have shown that sphingomyelins constitute less than 50 % of the value found with one of the most commonly used methods for sphingomyelin determination. Thus, at present there is little to be gained from a more detailed discussion of the sphingomyelin values of brain tissue reported in Niemann-Pick disease.

There was also an increase in cholesterol and glycero-phospholipids (lecithins and kephalins) in the affected organs. The most likely explanation of this accumulation is that these components are necessary for the formation of a stable lipoprotein structure in which form the sphingomyelins can be stored. The small proportion of esterified cholesterol (5 %) lends further support to the notion that cholesterol is engaged in the formation of a tissue lipoprotein structure Moreover the small amounts of triglycerides suggest the formation of a specific lipoprotein structure, possibly of the β type

Summary

Clinical and histologic findings in two siblings with the infantile type of Niemann Pick disease are reported. The clinical course was fulminant with early jaundice marked enlargement of the spleen and liver and death at 5 and 8 months. Vacuolated lymphocytes were found in the peripheral blood a small percentage of such cells were also found in the peripheral blood from the parents. The clinical picture may be ascribed to severe liver cell damage with Niemann-Pick cells, giant-cell transformation, fibrosis and bile stasis. The evidence suggests that the hepatic changes constituted the neonatal liver s non specific reaction to injury In one case an accumulation of lipo-pigment —probably ceroid—was noted in the lymph nodes this was considered a secondary feature due probably to the liver cell damage and the disturbance of lipid metabolism

Chemical analyses performed in one

case showed increased concentration of sphingomyelins in the spleen, liver lymph nodes and kidneys, normal concentration in the cerebral grey matter and decreased in the white matter In both cases the spleen showed a tenfold increase in weight and in one case there was a hundredfold increase in the sphingomyelin content Abnormally high levels of cholesterol and glycero-phospholipids were noted in the visceral organs only a small proportion of the cholesterol was esterified and the triglyceride content of the affected organs was low These facts provide some support for the view that the sphingomyelins in Niemann Pick disease is stored in the form of lipoprotein

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The White Blood Cell Count and the Erythrocyte Sedimentation Rate in Pertussis

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An increase in the total number of white blood cells in pertussis was first reported by Fröhlich in 1897 [3]. Since then several investigators have described a characteristic increase in the total white cell count associated with lymphocytosis [1 * 4 6 7 9]. Fairly thorough search of the literature however revealed no systematic studies of the leucocytes with regard to duration of the illness and the patient's age. It was therefore considered of interest t study white cells during the first weeks of pertussis. As Gold *et al* [4] suggested that the erythrocyte sedimentation rate might be of diagnostic value in the paroxysmal stage of this disease, the relation of this test to the patient age and the week of the disease was also studied.

Material

The material consists of children admitted t Flensburg Children Hospital, Malmö, with a diagnosis of pertussis during two epidemics, one in 1956–1957 (76 patient) and one in 1960–1961 (104 patients). Onl cases whose subsequent clinical course was typical were included in the present investigation. During the first epidemic no attempts were made to isolat the causal agent. During the second epidemic the cough plat culture was used in 52 cases and Bordetella pertussis was isolated in 11. Three hundred and seventy-one leucocyt counts and four hundred and twenty erythrocyt sedimentation rates were obtained. Nearly ll of the youngest children were admitted for the disease per se; some of the older children for complications, and most of the oldest because they could not be cared for adequat ly at home.

Satisfactory triple vaccination had been done in three cases, three received two injections, while seven received only one. In the 1956–1957 epidemic, tetracyclin had been given to 43% of the children and chlorom cetin to 26%. In the second epidemic, 72% received chloramphenicol, whil only one patient was given tetracyclin. In addition, during the first epidemic about one of every five patients was given at least one injection of immune globulin against pertussis. During the second epidemic about half of the children rece ed immune globulin, usually dose of 2.5 ml every other day (total dose 10 ml). Of the patient in the two epidemics, 27% and 18%, respectively received only symptomatic treatment.

Results and Discussion

Leucocyte

Th epidemics did not differ from one another regarding the total white cell count or the percentages of the variou types of leucocytes. The number of cells

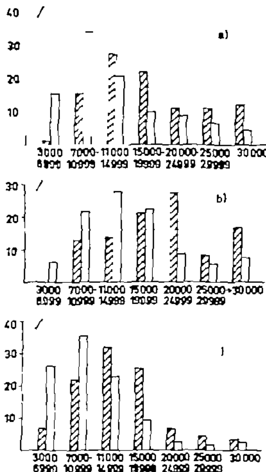


Fig 1 Frequency distribution of leucocyt counts (shaded columns) nd lymphocyte shaded columns) during first 4 weeks of ( ) First—second week (91 counts), (b) third week (161 counts) ( ) fourth week (119 counts).

did not appear to be influenced by either the type of antibiotic used or the injection of immune globulin As only a few cases received triple vaccination no con clusions are warranted on its effect on the blood picture In view of these similarities, pooling of the results obtained in the two series was considered justified.

The total white cell and lymphocyte counts noted within the first two in the third and the fourth week of disease are shown in Fig 1

It is evident from Table 1 that in pertussis the white blood cell picture in children below 6 months differed from that in the older age groups. The leucocyte count is normally higher during the first half year of life Therefore in these young infants, the total number of leucocytes and the number of lymphocytes were said to be increased and suggestive of pertussis only when they exceeded 20 000 and 15,000 per mm³ respectively Within these limits definite leucocytosis was noted in 23 % and lymphocytosis in -1 % during the first two weeks of the disease The corresponding figures for the third week were 25 % and 19 %, but during the fourth week neither of these values was increased. The findings largely agree with the results obtained in previous investigations in which leucocytosis in pertussi wa not common in this young age group [1 7]. The present investigation argues against the conception that characteristic changes in the white blood cells are invariably absent in pertussis in such young infants [9] It also provides evidence against the assumption that the blood picture does not vary with age in this disease [9]

As to the children over 6 month (upper limit of normal range of variation of leucocytes and lymphocytes 15 000 and 11,000 respectively) 71 % had leucocytosis and 63 % lymphocytosis during the first or second week of pertussis In the third week the white cell count also supported the diagnosis of pertussis in about 80 (> 15 000 leucocytes in 81 „ > 11 000 lymphocytes in 83 %) In the fourth week characteristic changes in the number of white cells were less common, but even then definite leucocytosi and lymphocytosis were noted in about half of the

TABLE 1 *Distribution of leucocyte and lymphocyte counts in pat ents aged 0–5 months and 6 months–12 years*

Values given in italics are lymphocyte and leucocyt values arguing strongly for pertussis. All values are given as percentages.

No. of white blood cells		Age 0–5 months Week of disease			Age > 6 months Week of disease		
		1	3	4	1 2	3	4
< 11,000	Leucocytes	23	29	44	12	6	23
	Lymphocytes	67	54	94	37	17	49
> 11 000	Leucocytes	77	71	56	88	94	77
	Lymphocytes	33	46	6	*63*	*83*	*51*
> 15,000	Leucocytes	36	54	13	*71*	*81*	*49*
	Lymphocytes	*21*	*19*	*6*	37	55	22
> 20,000	Leucocytes	*23*	*5*	*0*	42	64	20
	Lymphocytes	10	6	0	27	28	8
No. of counts		30	48	3_	5_	113	87

TABLE *Leucocyte and lymphocyte counts and erythrocyte sedimentation rate eight cases of pertussis with marked leucocytosis*

ESR values in mm/1 hr

Case no.	Age (months)	Sex		Week of disease					
					3	4	5	6	7
1	24	F	Leucocytes			54,900	33,400	21,300	
			Lymphocytes			42,000	27,000	12,500	
			ESR			17	7	16	28
2	16	M	Leucocytes	22,900	68,000	39,800	54 400		
			Lymphocytes	17 700	53,7*0	34,000	10,600		
			ESR	15	3	10	4	11	24
3	11	F	Leucocytes		54,200	23,700	31,600	24,200	
			Lymphocytes		45,700	16,300	19 700	14,200	
			ESR		30	14	16		
4	14	F	Leucocytes	50,500	47,800	20,300	16,700		
			Lymphocytes	41,500	42,900	18,700	10,000		
			ESR	10	10	9	21	12	
5	22	F	Leucocytes	71,600	40,000	20,500			
			Lymphocytes	56,200	36,200	14,200			
			ESR	30	18	14			
6	11	F	Leucocytes		54,800	44,200	19,900		
			Lymphocytes		42,100	3_,900	13,200		
			ESR		8	13	14		
7	13	F	Leucocytes			65,200	28,200	24,000	18,200
			Lymphocytes			56,400	22,800	17,200	10,900
			ESR			18	7	12	
8	16	F	Leucocytes		53,000	37,200	20,600		
			Lymphocytes		41,700	30,200	14,800		
			ESR		1	12	7		

TABLE 3 *Erythrocyte sedimentation rate during first 4 weeks of pertussis*

ESR (mm/1 hr)	Week of disease 1	2	3–4	No. of determinations	%
1–15	64	110	103	287	63.8
16–25	20	37	33	90	1 4
26–35	10	14	9	33	7.9
36–45	5	6	13	4	5.7
46–55		4		4	0.9
>55	1	1		2	0.4
No. of determinations	90	1	158	430	100.0

cases (>15 000 leucocytes in 48% and >11 000 lymphocytes in 51%). On subdivision of these patients into three age groups 6–11 months 12–23 months and 2–12 years, no differences were found in the white blood count and its variation with the week of the disease

An increase in the total white cell count to more than 50 000 per mm³ in pertussis is considered prognostically unfavourable and a sign of some complication often pneumonia [10]

Of these 180 patients marked leucocytosis was noted in eight (Table 2) aged 11 months to 3 years Seven of them were girls. The highest total count was 71 000 with 56,200 lymphocytes. Complications were observed in four cases (bronchopneumonia in two otitis in one and tonsillitis in one) This group included the only fatal case in the series (an 11 month-old girl with bronchopneumonia) In two of the seven survivors the pertussis was severe while in the remaining five the course of the whooping cough did not clearly differ from that in patients with moderate leucocytosis and lymphocytosis The average hospital stay for patients with marked leucocytosis was 4 weeks as against 3½ weeks for the entire material

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate measured by the micromethod of Strom [8] was not found to vary with age

The ESR in children with marked leucocytosis was on the average 14 mm/1 hr which may appear remarkably low (especially since half of the cases were complicated) but accords well with the findings of previous investigators [4]

It is clear from Table 3 that 63 of all values were below 15 mm/1 hr In 83 of the cases (82 in the first weeks and 80% in the third and fourth weeks) the ESR was less than 25 mm 1 hr The 63 determinations above 25 mm 1 hr (15 of total) were obtained in 48 patients Of these 26 had complications In this group, therefore the frequency of complications was 54 in contrast to 18 in the group with an ESR of less than 25 mm 1 hr Five of the 6 patients with an ESR above 45 mm/1 hr had complications

In uncomplicated pertussis the ESR does not as rule appear to be substantially increased or to vary from one week to another of the disease Knowledge of the ESR may therefore be of diagnostic value normal or subnormal level supporting the diagnosis of pertussis in suspected cases

Summary

The white blood cell count and the erythrocyte sedimentation rate were studied in 180 hospital patients with a clear-cut diagnosis of pertussis. In children below 6 months, the white blood cell picture favoured a diagnosis of pertussis in only one out of every four or five cases during the first 3 weeks of the disease but not later In children over 6 months, absolute leucocytosis and lymphocytosis were noted in the majority during the first 2 weeks of the disease (leucocytosis in 63 % and lymphocytosis in 71 %) During the third and fourth weeks changes in the white cells supported the diagnosis of pertussis in 80 % and 50 %, respectively Marked leucocytosis (more than 50 000 leucocytes per mm³ of blood) was noted in 8 cases. In uncomplicated pertussis the erythrocyte sedimentation rate is usually normal or subnormal and does not appear to vary with the patient's age or the week of the disease

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CASE REPORT

A Case of Giant Hemangioma with Thrombocytopenia

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On August 19, 1961 a 40-hour-old infant (D.S) was admitted to the Pediatric Clinic. Full term delivery had taken place at the Obstetrical Clinic of the University of Amsterdam (Director: Prof. Dr. G. J. Kloosterman) after an uneventful pregnancy during which the mother had suffered only an attack of bronchial asthma of a week's duration, and a short lasting fainting spell with melena without further known details, both occurring during the 5th month of pregnancy. The sole medication taken during pregnancy was neobenodine (-dimethylaminoethyl-4-methylbenzhydrylaether HCl), an antihistaminicum. In the period the child was under our observation we could ascertain that the mother did not have thrombocytopenia.

Delivery took place in persistent occiput posterior presentation for which manual correction had appeared to be impossible. Immediately after birth a bluish red colored, orange-sized tumor was visible in the left neck area. This tumor was solid on palpation and presented an irregular surface. The bluish red discoloration was present over an area larger than the tumor itself and in most places was not sharply demarcated. In the buccal cavity under the mucosa of the cheek, and near the frenulum linguae at the left side a few dilated tortuous veins were visible. There was no difficulty in respiration or swallowing.

Because of the apparent considerable hemorrhage in and around the tumor an estimation of the fibrinogen content of the blood was made and revealed that this, being 30 mg %, was notably lower than the normal value for this age viz. about 250 mg %. The prothrombin time was increased (19.5 seconds compared with a check value of 13.8 seconds) and the platelet count was 147 000/mm² (normal value at the time of birth is, according to Wintrobe, 180 000—250 000/mm³ [24]).

During the first twelve postnatal hours the child received twice an intramuscular injection of 1 mg vitamin K_1. The hemoglobin content at the time of birth was only 11.. g %. During the first postnatal day petechiae developed over the whole body, particularly on the scalp. With these symptoms the child was admitted to the Pediatric Clinic.

The tumor did not appear to have been growing but now the child showed a considerable jaundice with a bilirubin value of 10.2 mg % 40 hours postnatally. This bilirubinemia, mainly due to an increase of the indirectly reacting bilirubin, was caused partly by an A-O antagonism (immuno-antibodies anti A and anti-A hemolysins could be demonstrated in the mother's blood), and partly could be explained by hemolysis in the subcutaneous hemorrhage. On the 5th postnatal day (Fig. 1) the bilirubin level was at its highest with 18 mg % and after this gradually returned to normal. No signs of kernicterus could be demonstrated at this or at any other time. No hepatic or splenic enlargement could be felt.

Once more an estimation of the fibrinogen content of the blood was made and this proved to be 100 mg %; it was therefore decided to give the child intravenous fi-

brinogen t an amount of 800 mg in an 1% solution. The next day the fibrinogen level was normal (280 mg%) and it was still nor mal 9 days later (290 mg%). Loss of blood alone does not seem to be the cause of ac quired hypofibrinogenemia, but this acqui red sort of hypofibrinogenemia parallels the degree of shock and possibly its duration [5]. In our patient no signs of shock were observed.

A fibrinogenopenia combined with excessive hemorrhage and mostly with shock, was found in similar cases by some other investigators [4, 9]

The platelet count of 8000/mm (Fonio method) was now distinctly decreased and remained t this level during several weeks, while the petechiae and othe symptoms of hemorrhagic tendency gradually subsided. On closer examination soft systoli murmur became audible over the tumor which presented clue t the probabl etiology of the tumor

Survey of Literature

Clinical aspect

In 1940 Kasabach & Merritt were the first to describe the syndrome of giant hemangioma with thrombocytopenia [14] Since then about 55 cases have been reported in the literature (of which 40 are reviewed here) mainly concerning infants and young children, but in a few instances adolescents and ad lts.

In seven cases the tumor was localised in the neck [.. 8 10 13 19 20], like that reported here. Likewise these tumors were present at birth or appeared during the first weeks after birth The size of these tumors corresponded also very well with ours.

The remaining cases showed great differences in nature and localisation The constant findings, constituting the bove-mentioned syndrome, are

(a) the extent of the hemangiomatous growths
(b) a thrombocytopenia, correlating with a decrease or disappearance of the tumor by any form of treatment and
(c) hemorrhage and anemia.

There is great variation in the seriousness of symptoms; generally speaking however the disease cannot be regarded as harmless. Of the cases mentioned, in eleven a serious hemorrhage occurred. Nine patients died six of which were due to hemorrhage In four cases the tumor growth showed malignant characteristics [8 15 20 22].

Histological aspect

From the descriptions, confusion in the nomenclature of the hemangiomas is apparent

Owing to the hemorrhagic tendency biopsy from the tumor is usually not possible. Where this wa possible th pathological diagnosis varied widely Sometimes the uthor gives the name of hemangioma or hypertrophi hemangioma and sometimes capillary hemangioma is diagnosed.

Others speak of a partly capillary partly cavernous hemangioma In only two cases was a solely cavernous heman gioma mentioned and in quite a number we encounter the name hemangio-endothelioma

It seems that the hemangio-endothelioma can occur as a benign or as a malignant growth. This differentiation however is not one based on microscopi aspects but on clinical grounds Usually th capillary and cavernous types of hemangiomas are regarded as benign. It is

interesting that on three occasions, within the hemangiomatic tissue megakaryocytes were found [6 11 15].

Localisation

Apparently any tissue may harbor these tumors but very often the site is in the subcutis without involvement of the skin, which is unusual in the general behavior of hemangiomas Most of them are giant and solitary but there are descriptions of patients with multiple small hemangiomas and thrombocytopenia

It is doubtful whether we should regard the case as belonging to this syndrome with the pinpoint to lentilsized hemangiomas in the oral and nasal mucosa in other words telangiectasis, accompanied by a perhaps coincidental thrombocytopenia [3]

Theoretical background

A theory explaining the combined occurrence of the thrombocytopenia and the tumor has not been found yet. The concept of platelet-consuming intravasal coagulation has not been supported by facts, unless Blix s finding of a rise in platelet count after administration of anticoagulants [4] and the microscopic finding of some thrombosis in the tumor by others [10] are evidence supporting this view Labeled platelets (using Cr^{51}) however did not lead to significant increase in radio-activity over the hemangioma [4 7 18].

Beller & Rohrmann offer a theory in which they assume a parallelism with the fibrinogenopenia in abruptio placentae which is often also accompanied by thrombocytopenia. According to this



Fig. 1 Patient 5th postnatal day

theory fibrin and platelets are consumed by hemostasis in the tumor [2], so this seems also to be in contradiction with the above mentioned findings with Cr^{51} Evidence against the theory of platelet consuming in the tumor is also given by a case in which there was a severe thrombocytopenia 4 weeks before the development of two big hemangiomas [10]

In one case platelet antibodies have been demonstrated [1] In our patient there were no complete or incomplete platelet antibodies (Central Laboratory of the Blood Transfusion Service of the Dutch Red Cross director Prof Dr J J van Loghem Jr) and this finding has also been reported by others

Attention should perhaps also be paid to a possible endocrinologic explanation, the fact that almost all the patients were newborns and the statement that thrombocytopenia sometimes is related to the menstrual cycle [3 *4], may point in this direction. In only one case was there an estimation of estrogenic hormones, and no abnormalities were found [17].

Bone-marrow

Examination of the bone marrow of some of the cases revealed an inhibition in maturation of the megakaryocytes, although present in normal quantities. In several cases, as in ours, a convincing deficit in the number of megakaryocytes was found. Many other patients, however did not show any abnormality of the bone-marrow

When as a consequence of the treatment the platelet count in our patient had shown a rise we could xamine another specimen of bone marrow of the child. The megakaryocytes had increased in number when compared with the first examination.

Most investigators do not give an opinion regarding the cause of the anemia They may see this condition as secondary to the hemorrhage Only Stuber mentions the possibility that this anemia might be explained by n inhibition of the bone marrow and supports this theory with the fact that the anemia is of normochromic type and show a minimal rea tion to iron therapy [1] In our patient the serum-iron level was clearly low (42 γ) the anemia initially showing normochromic aspect becoming hypochromic in later stages Th number of reticulocytes repeatedly proved to be normal (concurrent with findings of others) The red-cell production was normal at two different examinations of the bone marrow

Therapy

Treatment of this disease varies greatly and includes X-ray and radium therapy cortisone and ACTH and anticoagulant administration local treatment with solid carbonic dioxide splenectomy surgical extirpation of the tumor and varying combinations of above mentioned methods. Evaluation of the results therefore presents difficulty particularly since spontaneous regression of the tumor probably also occurs, as might have been the case in a patient who showed a disappearance of the tumor and normalisation of the platelet count 17 months fter discontinuing treatment with cortisone and splenectomy at an even earlier date [6] and in a patient who recovered after treatment for 2 months with _ 5 mg prednison [7]. The recovery which was complete 2 years after splenectomy could also be considered spontaneous [23] Except total surgical removal and radiation other forms of therapy are regarded as unsuccessful. Recurrences were seen after radiation treatment, probably following low-dosage treatment and in many cases the observation period could not be regarded as sufficiently long to judge final results In one case only there was an observation time of six years [8]. This wa a little boy with a hemangioma in the right neck. very similar to that in our patient where therapy was by X-rays F llowing the first treatment (4 200 r) small hemangiomas were seen on ther parts of the body which disappeared

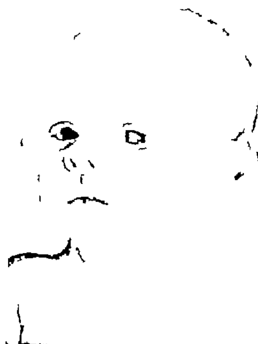


Fig — Patient just before the first X-ray t eatment (8 weeks old)



Fig 2. Patient two days after the last X-ra treatment (3½ months old)

during the second series of treatments (10 × 200 r) Following this a recurrence of the small hemangiomas was noted while the original tumor decreased steadily Two years after the treatment the large tumor the small hemangiomas and the thrombocytopenia had completely vanished After four years the skin at the site of radiation showed atrophic changes, while there was a slight bending of the clavicle and the head of the upper arm on the right side showed irregular bone formation. No other residual effects were noted.

When our patient was 8 weeks old the platelet count showed a spontaneous increase to 50 000/mm³ but the tumor had slightly increased in size (Fig 2) Since surgical extirpation of this tumor on account of its localisation and nature would present too many risks, X-ray treatment was started (Radiology Department, Binnengasthuis Dr E J Renaud Dr P Cohen and consultant Dr H J J Lokkerbol) Dosages used were: during 4 consecutive days a total of 400 r by two glancing field of 8 10 cm (180 kV) at 40 cm distance (0 9 mm Cu filter)

During the first 14 days after treatment was started, the tumor appeared to decrease in size while the platelet count fluctuated between 60 000 and 100,000 mm³ Following this period however the tumor started growing again at an even faster rate Therefore a month after the



Fig. 4 Patient eight months after the last X ray treatment (1 months old).

first series a second series was started now totaling 1500 r by two glancing field of 8 × 10 cm (180 kV) at 40 cm dist ance (0.9 mm Cu filter) during 10 con secutive days (Fig 3)

In the meantime the child received several transfusions of whole blood to combat the anemia. After the last X ray treatment had been given, in the course of 3 weeks, a considerable decrease in size of the tumor was seen. The platelet count reached normal values (*00 to 250 000/mm³) At the present eight months after the last X ray treatment was given no residual tumor can be palpated the platelet count has remained normal and no ill after-effects of treatment can as yet be demonstrated (Fig 4)

Summary

Description of a case of large hemangioma with thrombocytopenia, he morrhage, and anemia, reacting well to X ray treatment Forty nine cases from the literature are reviewed. These show great variation in the localization and histological findings clinical course and type of treatment. This disease should not be regarded as harmless in view of the possibility of serious hemorrhages and the not negligible chance of underlying malignancy An acceptable concept, com bining regression of the tumor and simul taneous increase in platelet count is not known. Until now radiation treatment and surgical removal of the tumor have been the only successful methods of treatment Where possible, surgical treat ment is to be preferred, since high doses f radiation seem to be required and relapses may follow In some cases spon taneous regression ppears to occur F brinogenopenia of not fully understood etiology has been noted in some cases.

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PROGRESS IN PAEDIATRICS

Difficulties and Dangers in the Management of Phenylketonuria

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The discovery of phenylpyruvic oligophrenia [11] was followed by the speculation that the metabolic disorder might cause the mental retardation, and that its correction could lead to an amelioration of the mental condition. This hypothesis was tested first by Bickel Gerrard & Hickmans [3], and in the ensuing years there have been several reports of the successful use of a phenylalanine low diet. The management of phenylketonuria is far from easy however and the problems which face clinicians when they encounter an example of this rare condition need to be discussed.

Screening Tests

The best results are obtained when treatment is started in infancy and screening tests have been developed to detect cases as early as possible [2, 4 10 12, 15 23]. The test used most frequently is the Phenistix test which consists of moistening a specially impregnated strip of paper with urine and noting the colour change

The test is easy but several precautions must be taken to avoid false negative results which is essential if any scheme for the screening of all babies is to be worth while For example it must be remembered that

(a) the nappy should be sufficiently wet to dampen the test paper rapidly yet not so soaking as to wash out the chemicals from it

(b) early morning specimens should be avoided, and

(c) the urine or nappy should not have been standing a long time Errors may occur through failure to take these simple precautions and such negligence is likely to result from boredom because so very many of the routine tests are negative

Confirmation of the diagnosis of phenylketonuria rests upon an examination of the blood. High plasma phenylalanine levels are characteristic and almost completely diagnostic of the condition, although the possibility that the high phenylalanine is associated with some other disturbance such as an abnormality of tyrosine metabolism, must be remembered [17]. Brimblecombe Blainey Stoneman & Wood [5] recorded the normal plasma phenylalanine values according to the different methods of estimation and drew attention to the fact that reports from different laboratories can be confusing if one is not

TABLE I *Protein calorie and phenylalanine contents of different low phenylalanine protein preparations*

Food	Calories	Protein g	Phenylalanine mg
	Composition per 100 g		
Lofenalac	450	15	80
Minafen	550	16	*0
Cymogran	400	40	10
Albumaid X P	370	36	Trace

aware that the normal values differ according to the method used.

Treatment

Once the diagnosis of phenylketonuria is made the question of treatment arises, and there is no doubt about the benefit which children under 18 months of age gain from treatment [16] although the results may not always be spectacular [18] Serious consideration should also be given to treating the older child whose intelligence may not be improved by it but who might be made much more manageable An example of a child showing this type of benefit is discussed later

The basic principles of the dietary treatment are simple all the natural sources of protein are excluded from the diet and replaced by a prepared powder which contains very little phenylalanine The administration of the diet can be considered in three phases. The first phase last about two weeks during which a phenylalanine-free diet is given and the plasma level falls to normal values The second phase consists of the addition of small quantities of phenylalanine usually in the form of milk because even a phenylketonuric child must have some of this essential amino acid The milk is increased until the patient is stabilized on the maximum quantity which can be tolerated without raising the plasma phenylalanine level The third phase consists of the substitution of portions of the milk allowance with other phenylalanine-containing foods in equivalent amounts to give greater variety and acceptability to the diet

When the diet was used at first complications such as oedema and anaemia

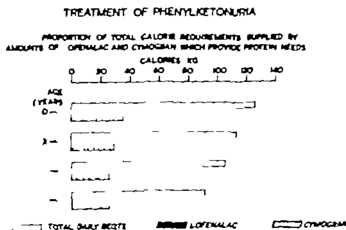


Fig 1 The proportion of the daily calorie requirement supplied by Lofenalac and Cymogran.

occurred fairly often, and status epilepti cus [14] and hypoglycaemia [9] were encountered. It is now possible to give a safer and better balanced diet but even so difficulties can still arise [20]

Several low phenylalanine protein preparations are now available but they differ in the calorie, protein, and phenylalanine concentrations (Table 1). These differences must be realised and taken into account in planning the diet. Two of these preparations Minafen and Lofenalac are practically complete foods and supply most of the total calorie requirements. They are designed for use with the younger child. If they are used for older children there is very little opportunity to add other items to the diet without exceeding the calorie requirements of the patient. This point is illustrated in Fig 1 where the proportion of the total calorie requirements supplied by Lofenalac is compared with the proportion supplied by Cymogran

Before starting treatment itself the place of treatment must be decided. In this country the answer is undoubtedly in hospital. This question might be thought unnecessary were it not for the fact that American experience is so much to the contrary Umbarger [21], for example stated a definite preference for home management and all ten patients reported recently by Centerwall and his colleagues [6] ere treated as out patients. The si tuation in this country however is such that hospital care is essential at least for the first t o phases of treatment The question can be extended to a considera tion of whether or not the patient should be transferred to a central hospital There is a tendency to collect cases of ny rare disease in centres where the st ff re ex



Fig 2. Case L, showing deterioration f control after the first year and also during ttack of measles.

perienced in the work. This has obvious advantages but because the treatment of phenylketonuria lasts for years and success with the diet in the home depends to a large extent upon close cooperation with the mother there are advantages in treating the patient as near to home as possible

Although the patient is in hospital for the first two phases of teatment it is the policy of most of us to change from in-patient to out-patient supervision for the third phase. This is the tim when most failures of treatment occur Success depends greatly upon the competence of the mother

Two cases illustrate the problems.

Case L (Fig 2) Treatment was started t the age of three months and was successful for a year As the child became more active and able t help herself to restricted foods, and the mother became more harassed by family chores and later pregnancies, the diet sl pped badly I an attempt to improve the home management, it was rranged that a Health Visitor should ttend the home each lay Assurance was given that the diet must be all right because the rine test was satisfactory It was not discovered for several week that the Health Visitor considered

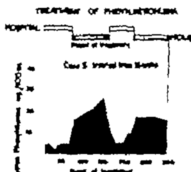


Fig. 2. Case 8, showing deterioration of control at home.

that the aim of the diet was to keep the urine test positive. Fig. 2 also shows the effect of an attack of measles upon the control.

Case 5 shows the failure of home treatment even more clearly (Fig. 3). When the patient was in hospital the control was good but relapsed as soon as she went home because the mother just could not manage the diet.

In both these cases the dietary treatment was abandoned finally because there was no further improvement in the mental state and the only way to give the treatment satisfactorily was by having the patient *in hospital permanently*. The decision was reached with regret in the first case where treatment had started at *three months* but with less misgiving in the second patient who was 15 months old when treatment was started. Most physicians who have treated a few cases of phenylketonuria have encountered this problem of a mother who cannot manage the diet at home. Treatment in hospital indefinitely is not feasible but if the diet could be relaxed after a few years hospital care during this time would be a reasonable proposition. The duration of treatment is one of the most important questions to be solved at the present time and a recent report is encouraging [13]. Three patients were treated from the neonatal period to 4 years and then given an unrestricted diet. No deterioration was detected in either the physical or mental states during follow up periods of 1 years, 1½ years and two months respectively.

In contrast to the previous cases where the mother's care is good treatment at home can succeed when the hospital has failed.

Case 1 was three years old, and was already retarded and hyperkinetic. It was decided to treat him in order to improve his behaviour. He was admitted to hospital in order to start the diet but he would not cooperate. *Within a few days he was the despair of the* medical and nursing staff. His mother said he would try to introduce the diet at home and succeeded completely within a week. *His response was much better than had been hoped and fully justified the decision to start* treatment.

The fact that treatment is started in hospital means that the infant's feeds are subjected to the process of terminal sterilisation. This *occasionally* produces a darkening of the feed which may distress both the mother and the nurses and if it is given to the baby may cause diarrhoea. It is important to make sure that the feeds are not overheated, or heated for too long when being sterilized so that this change does not occur. The appearance of the feed is important for its acceptability [7].

In the early stages when the baby is on bottle feeds it is fairly easy to give the diet. It is more difficult later when greater variety is required. In order to achieve this variety portions of the milk allowance in the diet are replaced by other foodstuff. The best results are obtained by using *fruits and vegetables* [6], and

this is right if for no other reason than that the concentration of phenylalanine is low in these foodstuffs and any error in the measurement of the amount to be given is not going to be too serious. Errors are more likely to occur if domestic measures other than weights are used. Two small observations confirm this point (Table 2) In one case the feeds were made up by spoon measures Several nurses made up the feeds and their spoonful when weig hed varied considerably The second observation arose from a comparison of the list of dietary substitutes given by Cen terwall *et al.* [6] with that given by Brimblecombe *et al.* [5] The former gives the quantities in domestic measures in keeping with the greater use of these measures in America than in this country and with the fact that the lists were prepa red for use in the home. In contrast, the quantities in the second list are given by weight, an obviously accurate method for use in a hospital. I asked the hospital dietician to measure out several foodstuffs from Centerwall s list which would con tain the equivalent of 20 mg of phenyla lanine These quantities were weighed, and these weights were compared with the weights expected according to the second list. The weights did not always agree and sometimes *the discrepancy was quite* marked

No matter how carefully th diet is planned, frequent examinations of the patient are necessary to ensure that the diet is adequat for growth and that oedema and anaemia are not developing and that it is sufficiently restrictive to keep the plasma phenylalanine in the normal range Monthly blood checks are usually recommended [5] but as one

TABLE 2. *Discrepancy between two d fferent methods of calculating the milk substitutes in the d et*

The weights of foodstuffs reputed to contain the equivalent of 20 mg of phenylalanine according to Centerwall *et al* [6, 7], using domestic measures are compared with the weights given in the diet used by Brimblecombe *et al* [5].

Food	Domestic measure	Reported weight, g	Actual weight of measure g
Banana	4 tablespoons	36	174
Orange juice	4 tablespoons	66	60
Carrot	1/3rd large one	76	50
Tomat	1/3rd small one	103	23
Cornflakes	1/5 breakfast cup	6	7

patient became quite hysterical after two years of this and could not be brought near the hospital, it is suggested that blood tests should be done much less often after the first year of treatment provided that the mother has managed the diet satisfactorily during this time The mother should be given a supply of Phenistix and be asked to test the urine each day and to report at once if there is any colour change. This method is not as precise as the blood test, but even with the blood test we know the situation on only one *day each month, and we do not yet know* the best time of day to take the blood test [18]

The early treatment of phenylketonuria is important but it can be dangerous. Serious complications of early treatment have occurred in Bristol, London and Australia [8], and only abandonment of the diet prevented a fatal outcome in som cases. The following is an illustrative case history



Fig. 4 Case A, showing the clinical deterioration and ultimate death with very early treatment

Case A had an older sibling with phenyl ketonuria. He was treated from the first feed because there was a good possibility that he would be affected. The fact that he was an affected infant was confirmed when he was a week old by substituting ordinary milk feeds for the diet for three days and noting the precipitous rise of the plasma phenylalanine (Fig 4). (Diagnosis before birth by examination of the mother's blood is not reliable because even if the plasma phenylalanine is raised this may be due to the fact that she is a heterozygote and need not mean that she is carrying an affected foetus. The cord blood of affected infants is *also reported to be normal [1]) The continua*tion of treatment after the short break to confirm the diagnosis produced vomiting and loss of weight. An extensive excoriation of the skin appeared and the infant developed fulminating pneumonia. The baby died despite the cessation of the diet

This complication of very early treatment has occurred with Minafen but not to my knowledge with Lofenalac. One suggested explanation is that these two preparations differ in their content of fatty acid and that the symptoms are caused by a deficiency of essential fatty acids [18]. Another suggested cause is a deficiency of vitamin E [6]. It is possible *however* that these complications are due to excessive restriction of the phenylalanine and in this connection *it is* worth noting that Lofenalac contains four times more phenylalanine than Minafen. A figure which is often quoted for the minimum phenylalanine requirement of an infant on a phenylketonuric diet is 25 mg/kg/day. This figure probably originated from the report of Paine & Hsia [19], but it is misleading because it was obtained from balance studies on one patient, and the authors emphasized that it is considerably less than the figures quoted for normal infants [22] (minimum 60 mg *normal 90 mg/kg/day*). The important point is that treatment in the neonatal *period is difficult and hazardous because* so little is understood about the nutritional requirements of infants. It is far bet*ter to abandon the diet temporarily if complications occur than to risk the life of the* child.

Summary

The difficulties and dangers encountered in treatment are described and it is concluded that careful and constant attention is necessary to obtain satisfactory results.

Acknowledgements

This paper was presented at Symposium on *Phenylketonuria* held at Manchester in February 196_, and is reproduced with the consent of the President of the Manchester Paediatric Club

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BOOK REVIEWS

J. Lauweryns: De Longvaten. Architectoniek en rol bij de longontplooiing

Arscia Uitgaven, Brussels, 196.. 303 pp., 77 illus. Price 590 Frs. Belg.

This book reports parallel microangiographic and histologic studies on the pulmonary vessels of dog and man with special regard to different types of bronchopulmonary arterial and arteriovenous anastomoses. The author maintains that there are no fundamental differences between the pulmonary angioarchitecture of dog and that of man. Lauweryns has further studied the degree of pulmonary expansion after injection of the pulmonary artery and has found "that primary atelectatic fetal lung can expand and show a normal alveolar structure—as after respiration—after injection of the pulmonary artery as far as its terminal branches whereas lungs in secondary atelectasis (with or without hyaline membranes) do not expand after injection which support the hypothesis of pulmonary capillary erection presented by Jävikä in 1958. The book (including figure legends) is written in Dutch, which language is not mastered by the reviewer. There is a number of photomicrograph... of high quality and a detailed summary in English and French. One drawback is that microangiographs and histologic pictures of individual anastomoses are not presented in parallel which should have been possible with the method used for the study. This to some extent reduces the conclusive evidence of the data presented. To judge from the summary and the illustrations no more important new findings are reported, but it is nevertheless to be regretted that an extensive work in this important field ... not published in a more accessible language.

Bengt Robertson, Stockholm

James Robertson: Hospitals and Children.

Victor Gollancz Ltd. London, 19..

About ten years ago a research worker in the Child Development Research Unit of the Tavistock Clinic in London, James Robertson, became a much debated person by producing a film called "A Two-Year-Old Goes to Hospital". It illustrated very clearly what these great changes mean to a small child and the risks that are involved when these changes occur. At that time he encountered strong resistance from his medical colleagues, but today certainly no pediatrician would deny the occurrence of such risks. Robertson found, however that his opinions and experience had very little support. He thus wrote a couple of newspaper articles and even made a television program in an attempt to engage the general public in the debate ... that their opinions were just as important as those of the medical profession. This resulted in an avalanche of letters, many of which are published unabridged ... small book by Robertson. It constitutes reading of the most interesting kind for all hospital doctors. We all agree upon the fact that the mother and child are a unit which if possible should not be split up, but we make ... before the practical difficulties that can arise from letting the mothers live in the hospital together with their sick children. Having read Robertson's book, with a description of how a child's stay in the hospital can be at its best and also at its worst, one becomes still more convinced that an increased interest in this field and intensified experimental activity are tasks of the greatest importance for the medical care of children.

John Lind, Stockholm

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From the Children Department and Pediatric Research Laboratory Rikshospitalet, Oslo

Plasma Erythropoietin Levels in Cord Blood and in Blood During the First Weeks of Life[1]

by S HALVORSEN

It is now generally accepted that humoral factors, erythropoietins play an important role in the regulation of erythropoiesis. The formation of these specific erythropoiesis stimulating factors is controlled by the relationship between oxygen supply and tissue oxygen requirement. Hypoxia be it anemic or hypoxic stimulates the production of erythropoietins and these again mediate the specific requirements for erythrocyte production to the bone marrow and thereby establish a level of erythropoiesis commensurate with oxygen needs for normal cellular metabolic activity [7 17 23 28] Erythropoietin probably acts by stimulating differentiation of primitive undifferentiated mesenchymal cells (stem cells) to erythroid cells [1 6], although different sites of action have recently been proposed [3]

Whether or not this regulatory mechanism is responsible for all adjustments of erythropoiesis is not known. This is partly due to the fact that the available methods for erythropoietin determination are relatively insensitive and that the presence of erythropoietin in plasma of individuals with normal hemoglobin has not been ascertained. Stohlman [29] has postulated that the erythropoietins function following rather severe hypoxic stimuli while other mechanisms are responsible for smaller variations in erythropoiesis, and Borsook *et al* [3] support this view This dual mechanism theory is, however not generally accepted [18].

In fetal life in the newborn period and during the marked changes in erythropoiesis following birth the role of the erythropoietins is partially unknown. It is therefore of interest to study the plasma erythropoietin levels in these physiological conditions. Such knowledge may also contribute to the understanding of the variations in erythropoiesis during this age period.

The marked changes in erythropoiesis during the first weeks of life have been studied by many investigators. It was demonstrated early that the hemoglobin and the red blood cell counts were elevated at birth and fell to subnormal adult levels during the following weeks [37]. These findings and the frequent observation of jaundice in the newborn period were the basis for the hypothesis of increased hemolysis following birth [15]. The question of red cell survival time in this age group is fundamental for this hypothesis. Studies using agglutination techniques [30] and

[1] This paper was in part read before the International Congress of Pediatrics, Lisbon, 1962.

Isotope studies [10, 21, 27, 41] have shown a normal or a slightly reduced survival time but the reduction has been so small that this cannot be the cause of the postnatal fall in hemoglobin and erythrocytes.

Investigations on erythrocyte production by means of reticulocyte counts [33], bone marrow studies [11, 14, 36] and Fe^{59} erythrocyte uptake [13] have shown that the erythropoiesis is very active at birth and decreases to subnormal adult levels within a few days. Two different hypotheses have been based on these observations. *1*) The decrease in erythropoiesis following birth is due to a bone marrow failure [9]. *2*) The decrease in erythropoiesis following birth is an adjustment to an environment with richer oxygen supply thus reducing the need for hemoglobin [12, 33].

Although most investigators in the field agree with the second hypothesis, others are not convinced and think it more likely that the bone marrow is functionally immature. Recently *Althoff & Werner* (*) postulated a failure in erythropoietin production as the cause of the post-natal decrease in erythropoiesis based on the finding of lower levels of erythropoietin in the plasma from erythroblastotic infants exchange transfused after the second day of life than shortly after birth.

The question of whether the regulation of erythropoiesis is mediated through erythropoietin in this age period or not is fundamental for the understanding of the changes in erythropoiesis following birth. Do erythropoietins participate in the regulation of erythropoiesis in the fetus and newborn infant as in later life? What are the plasma erythropoietin levels in cord blood and during the first weeks of life? Do the fetus and newborn infant respond to hypoxia with increased production of erythropoietins? It is the purpose of the present paper to report investigations on these problems.

Material and Method

Cord blood from 16 healthy newborn infants was investigated. One mother was Rh negative, all the others were Rh positive and none of the infants showed any sign of erythroblastosis. The deliveries were spontaneous and uncomplicated except in one case with protracted labor.

During the first week of life blood was taken by venipuncture from six of the above mentioned infants and nine other infants. The hemoglobin was normal for the age and weight group in all infants. Three infants weighed less than 2500 g at birth. In two cases blood was collected at the beginning of an exchange transfusion because of hyperbilirubinemia without anemia (Hb ?? g).

In order to study the erythropoietin response to hypoxia in the fetus, blood from erythroblastotic anemic infants was collected either at birth or at the beginning of an exchange transfusion performed shortly after birth. It has been considered that all these plasmas reflect the erythropoietin level in cord blood.

The erythropoietin response to hypoxia in the neonatal period has been investigated in four infants with neonatal erythroblastosis, and in three infants with cyanotic heart disease. The erythroblastotic infants had not been exchange transfused prior to investigation. The infants with cyanotic heart disease all died and the autopsies showed transposition of the great vessels in all three cases.

The blood samples were centrifuged shortly after withdrawal, the plasma pipetted off and either used immediately or stored at -20° C until used.

The plasma erythropoietin was determined using transfusion induced polycythemic mice as recipients (**) and Fe^{59} incorporation into the red cells as parameter [31, 35].

TABLE 1 *Control material*

Material injected	Dose ml	N of mice	Fe^{59} % uptake ± s.e.	Mean hematocrit
Normal saline	0.25 2	12	0.60 ± 0.14	64
Adult plasma	0.50 2	11	0.72 ± 0.25	63
Standard erythropoietin	0.012	3	12.20 ± 6.10	56
	0.025	4	26.30 ± 4.8	61
	0.075	3	51.40 ± 7.50	60

Table I shows the total Fe^{59} per cent incorporation in the red cells of polycythemic mice injected with normal saline plasma from an adult with hemoglobin of 14.8 g and standard sheep erythropoietin preparation[1] in three doses.

The standard erythropoietin preparation has kindly been supplied by the Hematology Study Section of the U.S. Public Health Service. The original 450 units of sheep erythropoietin was dissolved in six ml normal saline and stored at −20 C until used. As this special lot of erythropoietin (Lot 048) has lost more than usual of its activity by storage in the cold [16] the original figures in units are not tabulated.

Seven to nine-week-old male mice belonging to the White label Osl strain were used. On the first, second and fourth days of the experiments the recipient mice received packed washed homologous red cells intraperitoneally in total volume of between 2.0 and 2.5 ml. On the fifth and sixth days the plasma to be tested was given subcutaneously in an amount of 0.5 ml each day. Approximately 0.1 microcurie Fe^{59} dissolved in normal saline was given intravenously in tail vein on the seventh day and on the eleventh day the mice were anesthetized and blood withdrawn by cardiac puncture for counting. The hematocrit was determined in the same sample using a microhematocrit method. The mice were weighed at the end of the experiments, and the blood volume calculated as 8% of the body weight at the time of sacrifice.

The amount of washed red cells injected to produce polycythemia was higher than in previously described methods where reticulocytes were used as parameter [22]. Thus, one has been sure that the recipient mice stayed polycythemic throughout the experimental period. In addition the hematocrit was determined at the end of each experiment, and mice with hematocrit of lower than 52 were excluded [31]. A well type scintillation counter[1] with an efficiency of about 1 10⁶ c.p.m. per microcurie of I^{131} with gamma crystal and background of between 86 and 122 c.p.m. was used.

The 96 hour Fe^{59} incorporation was used as parameter. The plasma iron clearance is very slow in these mice [35] and it is essential either to use an incorporation time long enough to allow the plasma radioactivity to be minimal or to use washed cells for counting. As hemolysis occurs easily during blood sampling and washing, it was chosen to use a long incorporation time. The iron incorporation was expressed as the total erythrocyte uptake in per cent of the injected dose. This was calculated as follows:

Fe^{59} per cent uptake

$$= \frac{\text{Body weight} \cdot 8 \cdot \text{sample count} \cdot 100}{\text{Sample weight} \cdot 100 \cdot \text{count injected}}$$

Results

Table 1 shows the results of the control experiments. Twelve polycythemic mice were injected with normal saline and eleven polycythemic mice with plasma from a

[1] SC-41 Autoscaler Tracerlab inc. Boston, Mass. U.S.A.

Table 2 *Plasma erythropoietin levels in cord blood*

Infant	Birth weight g	No. of mice	Fe⁵⁹ % uptake ± s.e.
R.M.	3850		0.37 ± 0.06
B.R [1]	4380	4	0.39 ± 0.10
A.L.	3440	6	0.53 ± 0.30
R.G	4030	4	0.60 ± 0.20
L.A.	3140	4	0.66 ± 0.17
S.L. [1]	2690	4	0.97 ± 0.76
L.W	3990	1	1.19
R.K.	3800	3	1.–1 ± 0.36
A.L.	3830	5	1.–1 ± 0.41
J.K.	3490	4	1.34 ± 0.71
R.H.	3700	4	2.01 ± 2.01
R.T [1]	3680	3	2.10 ± 2.37
C.M.	3360		3.41 ± –.87
K.J [1]	3940	5	4.07 ± 2.62
W.L.	3230	3	6.13 ± 3.77
N.P [1]	3390	3	7.84 ± 3.13

*Mean weighted by number of mice 2.08 ± 0.42**

Table 2 shows the Fe^{59} per cent erythrocyte uptake of polycythemic mice injected with cord plasma from normal newborn term infants. In the infants with [1] attached to the initials plasma has also been tested during the first week of life. The results from the individual cord plasma assays are pooled and the weighted mean and the standard error of the weighted mean have been calculated. In this and the following tables the asterisk attached to the Fe^{59} incorporation values denote the significance of the difference between the value and the mean of the pooled neonatal plasma assays ($p \leq 0.01$).

normal adult with a hemoglobin of 14.8 g. In the same table the Fe^{59} erythrocyte uptake in polycythemic mice injected with a standard erythropoietin preparation[1] in three doses is also shown. The saline group show small variations, while the mice injected with normal plasma show greater variations. This is in accordance with previous observations on polycythemic mice using reticulocytes as parameter [24].

[1] The standard sheep erythropoietin preparation was kindly supplied by the Hematology Study Section of the U.S. Public Health Service (Lot K 147046).

Table 2 shows the results of the cord plasma assays. Some plasmas show definitely increased erythropoetic activity, others only a moderate increase, and some show no increase. In this small series it has not been possible to detect any relationship between erythropoietin level and birth weight, age of mother, duration of delivery or length of gestation.

Table 3 shows the plasma taken from infants during the first weeks of life, the age at which the plasma was withdrawn and the hemoglobin and reticulocyte levels at that time. None of the plasmas taken during the first weeks of life from infants with normal hemoglobin show any erythropoietic activity.

In both Tables 2 and 3 the results of the assays from different plasmas are pooled, and a significance test has been performed versus the saline controls and between the pooled cord plasma and neonatal plasma.

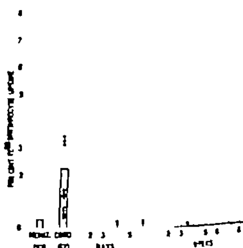


Fig. 1. Plasma erythropoietin levels in cord blood and during the first weeks of life. The columns represent the mean of the pooled cord plasma assays (Cord) and neonatal plasma assays (Neonat.) and the number below the columns the total number of the recipient polycythemic mice.

TABLE 3 *Plasma erythropoietin levels during the first weeks of life*

Infant	Birth, weight g	Age days	Hb g	Retic., %	No. of mice	Fe^{59} uptake ± s.e.
B.R.[1]	4590	1	20 0	3.5	4	0.29 ± 0 05
K.J.[1]	3940	2	20.0	3..	5	0 18 ± 0.01
N.P.[1]	3900	3	20.0	3 2		0.61 ± 0.23
K.B.	3330	3			3	0 30 ± 0 03
R.T.[1]	3480	4	20.0	0.9	3	0.17 ± 0.01
W.J.	3800	4	20 0		4	0 24 ± 0 02
S.L.[1]	2000	5	18.4	0.9	2	0.24 ± 0.01
M.H.	1820	6	20.0		4	0 24 ± 0 03
B G.	3150	6	19.3		5	0.19 ± 0.02
C.N.	1870	7	20.1	3.9		0 66 0.29
H.J.	1 80	8	20 0	1 7	3	0 23 ± 0 04
J.S.	3370	24	19.3	0.4	3	0.11 ± 0.01
H.S.	2060	38	14 6	0.3	3	0.29 ± 0 14
A.V.	1500	51	9.3	4.5	4	0 27 ± 0.06
W.K.	3480	54	16.2	0.6	5	0.28 ± 0 06
Mean weighted by number of mice						0.30 ± 0 04

Table 3 shows the Fe^{59} per erythrocyt uptake of polycythemic mice injected with plasma from infants during the first weeks of lif (Neonatal plasma assays). The initials of the infants, the birth weight and the age in days, the hemoglobin and the reticulocyte values at the time of blood sampling are also tabulated The results from the single plasma assays hav been pooled and the weighted mean and the standard error of the weighted mean have been calculated.

groups. The difference between the cord plasma group and the saline group is not statistically significant while the dif ference between the cord plasma and neonatal plasma group is highly significant ($p < 0\ 001$). Fig. 1 shows the distribution of the Fe^{59} incorporation in the red cells of polycythemic mice injected with cord plasma and plasma from infants during the first weeks of life.

In Table 4 the erythropoietin levels in plasma from erythroblastotic infants shortly after birth are tabulated. Th table also shows the hemoglobin in cord blood, the reticulocyte percentages shortly after birth and the time at which the blood

TABLE 4. *Plasma erythropoietin levels in erythroblastotic fants shortly after birth*

Infant	Age hr	Hb, g	Retic., %	No. of mice	Fe^{59} % uptake ±
P O.	1	8 4	14.0	2	44.28 ± 12.10*
O.F.	1	8 0	40 0	4	24.87 ± 3.83
B.T.	4	11.2	11.6	4	2.22 ± 0.46*
L.J.	0	14 5	2.8	2	1 72 ± 0 78*

Table 4 shows the Fe^{59} per cent erythrocyt uptake in polycythemic mice injected with plasma from erythroblastotic infants taken shortly after birth. The age of the infant at the time of blood sampling, the hemoglobin in cord blood and the uncorrected reticulocyte values are also tabulated.

TABLE 5 *Plasma erythropoietin levels in hypoxic infants during the first weeks of life.*

Infant	Age days	Hb g	Retic %	No. of mice	Fe^{59} % uptake ±
Anemic hypoxia					
A.L.	1	9.4	4.0	5	1.28 ± 0.56
B.O		5.0	6.8	5	11.80 ± 2.87
B.O	15	8.5	1.4	3	2.37 ± 0.7
A.E.	2	16.0	5.5	4	2.19 ± 1.08*
Hypoxic hypoxia					
B.G	13	20.0	6.4	4	13.89 ± 2.33
P.N	10	17.3	6.2	2	22.30 ± 2.10*
F.L.	22	20.0	4.2	4	27.48 ± 2.67*

Table 5 shows the result of the plasma erythropoietin assays of blood withdrawn from anemic infants (anemic hypoxia) and from cyanotic infants with transposition of the great vessels (hypoxic hypoxia).

was collected. The data show that severely anemic infants may have markedly elevated erythropoietin levels at birth.

Plasma from hypoxic infants taken during the first weeks of life has also elevated erythropoietin levels. Table 5 shows that plasma from both anemic infants and cyanotic infants with transposition of the great vessels significantly increases the iron uptake in polycythemic mice. In both Tables 4 and 5 the asterisks attached to the values of Fe^{59} uptake denote the significance of the difference between the actual value and the mean Fe^{59} per cent uptake of the pooled neonatal plasma assays.

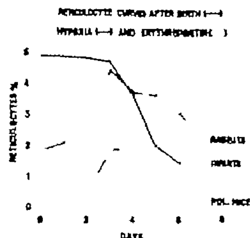


Fig. 2. Reticulocyte curves in infants during the first week of life [34], in infant rabbits following eight hours hypoxic hypoxia [40] and in polycythemic mice following a single injection of erythropoietin [6].

Comments

Previous methods for erythropoietin determination have been relatively crude and insensitive, but during recent years the techniques have been markedly improved. The transfusion induced polycythemic mouse is generally accepted as the most reliable recipient animal, and the introduction of Fe^{59} erythrocyte uptake rather than reticulocyte counts has made the method less time-consuming and more sensitive. With this method it is possible to detect smaller amounts of erythropoietin than with the starved animals previously used [31]. Although

the method gives reproducible results, it must be admitted that small increases in erythropoietin may still be undetectable. The most serious disadvantage of this, as of all assay methods for erythropoietin is the rather great variation in response from animal to animal even to standard preparations of erythropoietin. However considering the consistency of the results in the control groups and the neonatal group, and the large deviations from these values in the pathological states, the data presented should give a reliable index of the humoral erythropoiesis regulatory mechanism in the fetus and newborn infant.

Erythropoietin levels in cord blood have been studied by several investigators [4 5 29] but the methods have been criticized [17] and Gordon [17] has stated that only the studies of Althoff & Werner [ ] are conclusive. These authors found that cord plasma from three normal newborn infants increased the reticulocytes significantly in intact rabbits when injected over four days with a daily dose corresponding to 18 ml/kg body weight of the recipient animal. The same authors also demonstrated elevated levels of erythropoietin in plasma from erythroblastotic infants taken at the time of exchange transfusion, a finding which has later been confirmed by Jones & Klingberg [*6].

The present study confirms the findings of Althoff & Werner of elevated erythropoietin levels in cord blood from normal infants. The increases found in the present study were however relatively small. There were also great variations from case to case. This may be due partly to the small number of recipient animals in the different series. However such differences are commonly found in investigations on erythropoietin levels in clinical material [40]. It is also possible that the functional status of placenta and different degrees of hypoxia during labour may influence the erythropoietin level in cord blood. In the small series presented no correlation between the duration of delivery length of gestation or age of mother and erythropoietin level in cord blood was found.

The studies on cord plasma from anemic erythroblastotic infants show that the erythropoietin levels may be markedly increased in anemic fetuses. The same is found in plasma taken at the time of exchange transfusion within a few hours of birth. These findings clearly demonstrate that the fetus responds to anemic hypoxia with increase in erythropoietin production, and that this humoral regulatory mechanism is intact during the last part of intrauterine life. It may be argued that the erythropoietin in fetal plasma may be transferred from the mother but this has to the author's knowledge no experimental basis. The finding of elevated plasma erythropoietin levels in pregnant women [19] does not necessarily favour this hypothesis but is more likely to be due to the slight anemia of pregnancy. On the other hand Jacobson *et al* [25] have shown that erythropoiesis in the offspring of polycythemic mice proceeds at a normal rate. The polycythemic mouse has no erythropoietin in its plasma and no signs of active erythropoiesis in the bone marrow and, at least in the mouse the fetus produces erythropoietin itself.

Systematic investigations on erythropoietin levels in the newborn period have not been reported previously. As pointed out such knowledge is essential for the

understanding of the changes in erythropoiesis in this age period. The study shows that there is no detectable erythropoietin in plasma from non hypoxic infants during the first weeks of life. Hypoxic newborn infants are, however capable of producing erythropoietins. Both infants with anemia due to erythroblastosis and those with hypoxia due to congenital cyanotic heart disease respond with increase in plasma erythropoietin. Especially the cyanotic infants are a clearcut proof of this, both because of the magnitude of the response and because they have no impairment of erythropoiesis in other respects. The present study does not rule out an incomplete failure of erythropoietin production in the newborn period but the finding of slightly elevated levels at a hemoglobin level of 0.4 g does not fit well with such an assumption, because even in the adult the erythropoietin level is normal or only slightly elevated at this hemoglobin level [40]. Althoff & Werner's finding of elevated plasma erythropoietin in an infant with a hemoglobin of 10.7 g who was exchange transfused for the second time at the age of seven days, is open to similar considerations.

The fetus lives in an environment of lower oxygen tension than normal adults [38]. The finding of elevated erythropoietin levels in cord blood is consistent with an oxygen deficit in utero. As some of the infants had no demonstrable erythropoietin or only slightly elevated erythropoietin levels, one must assume that many fetuses have reached an approximate equilibrium between oxygen need and oxygen supply.

Following birth there is, under normal conditions, an almost immediate improvement in the oxygenation of the blood and adult levels for oxygen tension are reached within three hours of birth [38]. The finding in the present study that no erythropoietin is detectable in plasma from normal newborn infants aged one day or more is another confirmation of the concept that the decrease in erythropoiesis following birth is due to the improved oxygen supply thus reducing the need for hemoglobin. If the post-natal decrease in erythropoiesis was due to bone marrow failure one would have expected high erythropoietin levels as found in hypoplastic anemias. On the other hand, the present study also shows that the decrease in erythropoiesis is not due to a failure of erythropoietin production as it is shown that neonates are capable of producing erythropoietins in response to hypoxic stimuli.

The delayed fall in erythropoiesis following birth is also in accordance with this hypothesis. In newborn infants the reticulocytes remain high for the first three days and then rapidly fall to subnormal adult levels [33]. The reticulocyte peak in intact rabbits following hypoxia is reached about the third day [20] and in the polycythemic mouse following an injection of a standard erythropoietin preparation between the third and fourth day [8]. These findings are illustrated in Fig. 2 where it is clearly shown that the time when the reticulocytes start to fall after birth corresponds very well with the time of the reticulocyte peak in experimental conditions following erythropoietin injection or erythropoietin production due to hypoxia. One can therefore assume that the production of erythropoietin stops within a few hours after birth. The findings in the present study confirm that the

thropoietins disappear from the plasma east within a few days of birth.

'rom the present study it may be con led that the erythropoietins are eleva in cord plasma at birth and that the s responds to anemic hypoxia with an reased production of erythropoietins s the erythropoietins play the sam damental role in the regulation of thropoiesis in the fetus as in later life lowing birth the erythropoietins fall to letectable levels in non-hypoxic in ts, and this is another confirmation of concept that the post-natal fall in thropoiesis is due to the improvement oxygenation following birth. Newborn ants respond to anemic or hypoxic hyp- a with an increase in plasma erythro- etin levels, and there is no demon able failure of production in this age iod. The general conclusion of the sent study is that the vital regulatory chanism of erythropoiesis through eryth poietin is intact in the lastperiod of rauterine life and in the neonatal riod.

Summary

Plasma erythropoietin levels have been idied in cord blood from normal and ythroblastotic infants, and in blood m normal and hypoxic infants during the first weeks of life. The erythropoietins are slightly elevated in cord plasma from normal infants and markedly elevated in plasma from severely anemic infants. No erythropoietin is detectable in plasma from normal infants during the first weeks of life while hypoxic infants have elevated plasma erythropoietin levels. It is con cluded that the vital regulatory me chanism of erythropoiesis through eryth ropoietins is intact in the last part of intrauterine life and in the neonatal period. The present findings are another *confirmation of the concept that the post* natal fall in erythropoiesis is due to an im provement of oxygenation following birth.

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From Alder Hey Children s Hospital, Liverpool

A Study of Specific E Coli Infections Occurring in a Unit for Surgical Neonates

by PETER D LAPATSANIS and IRENE M. IRVING

One of the most important aspects of the management of a ward or unit reserved for new born babies is the prevention and control of infection and the pathogenic E. coli are a notable source of trouble in view of the marked susceptibility of neonates to infection with these organisms.

The Neonatal Surgical Unit at Alder Hey Children s Hospital has proved no exception to this general rule Since it was opened in May 1953 outbreaks of E. coli gastro-enteritis have occurred with increasing frequency presumably due to the fact that pathogenic E. coli infections are now widely endemic in this region as compared to ten years ago

This paper is a retrospective study of some aspects of the incidence of pathogenic E coli infection in the unit during a period of approximately two and a half years (1st January 1959 to 31st August 1961)

Lay-out of the neonatal surgical unit

The Unit can accomodate nineteen infants. The ward is divided into three separate rooms, the main nursery containing ight cots or incubators, an air-conditioned "hot-room holding four incubators for premature infants and infants recovering from major surgery and a small ward for convalescent infants, holding four cots. In addition there are two isolation cubicles, one holding one cot and the other two cots. The distance between cots and incubators is three to four feet. The nursing staff consists of seven sisters one staff nurse and two or three junior nurses.

Babies coming from maternity units are admitted to the main ward unless there is any suspicion of contact with infection. Babies coming from home or a general paediatric unit are nursed in the isolation cubicles for several days and are only transferred to the main ward when the likelihood of infection has been excluded. All babies have faecal or rectal swabs cultured twice weekly Babies contracting a specific E. coli infection are, whenever possible, transferred immediately from the Unit to one of the medical isolation wards. A case with a positive swab which is considered from the surgical standpoint to be unfit for transfer is barrier nursed in one of the isolation cubicles on the Unit. When, as has occasionally happened, E. coli gastro-enteritis has affected several infants in the unit, admissions have had to be diverted to the general surgical wards, until such time as the Unit has been emptied and cleaned.

Scope of present study

Babies who proved to have non-surgical conditions have not been included in this study Babies dying within the first forty-eight hours of lif are also excluded because they are not considered to have had time or opportunity to acquire E coli infection

TABLE 1 *Numbers of babies admitted January 1 1959–August 31 1961*

Year	No. of babies admitted	No. with non surgical conditions	No. of deaths in first 48 hours of life	No. of surgical cases exposed to potential infection
1959	143	21	13	111
1960	189	12	16	161
1961	106	12	1	95
Totals	442	45	30	367

and death was invariably due to causes other than gastro-enteritis. The last column in Table 1 shows the numbers of babies with surgical conditions who are considered to have been exposed to potential infection.

Overall incidence of pathogenic E. coli infection

Of the 367 babies at risk, 54 (14.6 %) excreted pathogenic E. coli in their stools with or without symptoms of gastro-enteritis. The duration of excretion of the organisms varied from instances where only a single positive swab was obtained to instances where infants continued to have positive swabs for a number of weeks. Two infants were found to have positive swabs at the time of admission. Of the infected babies 22 (5.9 % of total) suffered from gastro-enteritis and 32 (8.7 % of total) were symptomless excretors at the time of swabbing (Table 2).

Five babies had what were regarded as two separate episodes of infection, i.e. a recurrence of positive swabs after three negative swabs had been obtained at intervals of two to four days, giving a total of 59 instances of infection in 54 babies.

TABLE 3 *Numbers of babies [illegible] excreting pathogenic E. coli*

Clinical group	No. of babies	Per cent age of infected babies	Per cent age of babies at risk
Babies with E. coli gastro-enteritis	22	41	5.9
Symptomless excretors of pathogenic E. coli	32	59	8.7

Incidence of pathogenic E. coli infection in different diagnostic groups

It will be seen from Table 3 that the highest incidence of pathogenic E. coli infection occurred in babies suffering from major abnormalities of the large intestine viz. Hirschsprung's disease and high rectal atresia. The difference in incidence in these two groups compared with the incidence in the other groups of cases was sufficiently marked to warrant further study which was pursued along the following lines.

1. We have examined the possibility that due to chance a larger proportion of babies with large intestinal abnormalities were patients in the Unit during outbreaks of E. coli gastro-enteritis than at other times. This, however, was not the case, the admissions in all groups being distributed fairly evenly throughout the period of the study.

2. The possibility that the "large intestinal" group was subjected to greater surgical stress and hence rendered more susceptible to infection was considered. As regards the cases of Hirschsprung's disease this possibility can be discounted as these babies were submitted to comparatively minor procedures viz. rectal biopsy, laparotomy and colostomy. As regards the cases of rectal atresia, three babies had had a colostomy only performed; four had had an abdomino-perineal "pull through" opera

tion, a procedure comparable in severity with the surgery of the oesophageal atresia group in which the incidence of pathogenic E. coli infection was significantly lower

2. The possibility that the differences in incidence in the different diagnostic groups could be related to their duration of stay in the neo-natal unit was next considered.

(a) Column 7 of Table 3 shows the average duration of stay of infected babies in each group at the time of the first positive swab and it will be seen that the figures for the Hirschsprung disease and rectal atresia groups are strictly comparable with the oesophageal atresia and small intestinal groups.

(b) As a further check w calculated the average duration of stay of all babies—infected and uninfected—in each group (column 6, Table 3) The average duration of stay in the rectal atresia (50 days) is considerably longer than that of the other groups; however three babies in this group stayed in the Unit for an exceptionally long time (230 days, 107 days and 162 days respectively) If these three cases are excluded the average stay of the remaining 18 babies is 28 days. Of these 18 babies, 6 were infected with pathogenic E. coli (33)

Incidence of symptoms in different diagnostic groups

In addition to the higher incidence of pathogenic E. coli infection in the large intestinal group it was noted that a higher proportion of infected babies in this group developed clinical gastro-enteritis than in the other groups. The figures, however are too small to be of statistical significance

Effect of treatment on excretion of pathogenic E. coli

Table 5 shows the effect of the first course of antibiotic or sulphonamide on the excretion of pathogenic E. coli. It will be seen that a significantly higher pro-

TABLE 3 *The incidence of infection by pathogenic E coli in the different diagnostic groups*

Abnormality	of babies t risk	No. with positive swabs for pathogenic E. coli: With symptoms	Without symptoms	Total	Ratio Babies with symptoms/babies without symptoms	Average duration of stay at time of first positive swab, days	Duration of length of stay in N S U days	% excreting pathogenic E. coli
Meningocele	10[illegible]	6	14	20*	1 2.3	30	23†	18
Oesophageal atresia	28	1	2	3	1	33	20†	10
Congenital abnormalities of small intestine	43	3	4	7*	1 1.3	45	32†	16
Meconium ileus	14	—	2	2	—	27	30	14
Hirschsprung disease	17	3		5	1 0.6	30	30	25
Rectal atresia	1	5		7	1 0.4	39	50‡	22
Anal atresia	16	1	1	2	1 1	11	14	12
Miscellaneous surgical conditions	12*	3	5	8	1 1.6	23	[illegible]	6
Total	26[illegible]	23	32	54	1 1.4	30	29	11.6
		χ^2 21.8			d.f. = 7	P = 0.005 (significant)		

In each of these groups one infant had positive stool culture on admission

† In each of these groups is included one infant who stayed in the unit for longer than three months.

In this group are included three infants who stayed in the unit for longer than five months.

TABLE 4 *Incidence of symptoms in different diagnostic groups*

Abnormality	No. with positive swabs for pathogenic E. coli: With symptoms	No. with positive swabs for pathogenic E. coli: Without symptoms	Ratio: Babies with symptoms/babies without symptoms
Congenital abnormalities of the large intestine	8	4	2:1
All other groups	14	28	0.5:1
	$\chi^2 = 3.03$	d.f. = 1	$P = 0.07$ (not significant)

TABLE 5 *Effect of treatment on excretion of pathogenic E. coli*

Babies excreting pathogenic E. coli	No. with negative swabs after first course of treatment	No. with positive swabs after first course of treatment	Totals
With symptoms	17 (77%)	5	22
Without symptoms	9 (38%)	15	24
	$\chi^2 = 5.86$	d.f. = 1	$P = 0.025$ (significant)

Eight of the 22 babies without symptoms were not treated.

Babies were regarded as being free from infection when they had three negative faecal or rectal swabs after treatment was discontinued, the interval between swabs being two to four days.

portion of babies with symptoms had "negative" stools after a single course of treatment than had symptomless excretors (77% and 38% respectively). Comparison of treatment in the two groups (Table 6) shows a greater uniformity of treatment in the group of babies with symptoms: this is because nearly all these babies were started on a course of Neomycin before the antibiotic sensitivities of the infecting organism had been obtained. Conversely in the symptom free group, treatment was less uniform because it could be delayed without risk until the antibiotic sensitivities of the organism were known. For the same reason, babies without symptoms started treatment on average forty-eight hours later than the babies with symptoms. As regards sensitivity to antibiotics dosage of drugs and duration of treatment there was no significant difference between the two groups.

TABLE 6 *Treatment of babies excreting pathogenic E. coli in their stools*

The numbers in brackets refer to the number of cases in which the organism was sensitive to the antibiotic given

Babies with positive swabs for E. coli	Neomycin	Framycetin	Chloramphenicol	Terramycin	Streptomycin by mouth	Sulphadimidine	Total
With symptoms	19 (1[illegible])	2^b	1 (1)				22
Without symptoms	16 (14)	2^a	1 (1)	3 (3)	1	1^b	24

a Not sensitive

b Sensitivity not determined

TABLE 7 *Incidence of different types of pathogenic E coli*

Type of pathogenic E Coli	No. of babies without symptoms	No. of babies with symptoms	Total	Ratio Babies with symptoms/babies without symptoms
0126 B16	9	7	16	1 1.3
026:B6	15	6	21	1 2.5
0111 B4	1	5	6	1 0.2
055:B5	2		4	1 1
0119:B14	3		5	1 1.5
0128:B12	2	0		—
0127 B8	3	0	5	—

Incidence of different serotypes of pathogenic E coli

In this study the serotype most frequently was E. coli 026.B6 only a small proportion of babies excreting this organism developed gastro-enteritis On the other hand five out of six babies infected with E. coli. 0111.B4 developed symptoms (Table 7)

Discussion

The high incidence of pathogenic E coli infection in the Neonatal Surgical Unit (14 6% of infants at risk) is considered to be due to the following circumstances.

1 The concentration in one ward of newborn infants. Before the establishment of the Unit in 1953 newborn surgical cases were admitted to general surgical wards where they not infrequently contracted gastro-enteritis by cross infection from older infants or children which was one of the factors which determined the establishment of the Unit (Rickham & Mason [2]) Despite the segregation of the newborn, E. coli infections have not been eliminated and having gained access spread rapidly and may be extremely difficult to eliminate

2. The fact that infants are admitted from maternity and paediatric units of many hospitals scattered over a wide area from any one of which infection may be introduced despite precautions at both ends. In many instances of outbreaks of E. coli infection in the Unit it has been possible to trace the source of infection to a hospital from which an infant has recently been transferred. This emphasises the necessity for more careful screening of infants at both transferring and receiving hospitals.

3 The fact that over one third of admissions are premature infants and all those included in the survey were submitted to operation, both factors which may be considered to lower resistance to infection

4 The fact that during the course of investigations, surgery and post-operative treatment these infants are subjected to a great deal of handling by both medical and nursing staff, thus multiplying the opportunities for cross-infection to occur In this series the incidence of symptoms in infected babies (41%) is surprisingly low when it is considered that 52 out of 54 infants were under three months of age at the time of infection.

Solomon and his co-workers in a study of 1 078 babies and children in eastern Massachusetts, the area from which most of the cases were admitted to the Boston Floating Hospital, found the overall sick carrier ratio to be 1:2 4 (3.3% had E. coli

gastro-enteritis; 5.6% were carriers). In the group of babies under twelve months of age however the ratio was 1:4:1 as compared with children over the age of one year for whom the ratio was 1:5.2 Novgorodska et al. investigated 4,546 babies and children in Leningrad during 1958–1959 and found that 10–20% were asymptomatic carriers of pathogenic E. coli, the rate varying from nursing home to nursing home and according to the age of the patients. In babies under twelve months of age the carrier rate was directly proportional to age ranging from 2.7 in the 0– month group (comparable in age to the infants in the present study) to 16 in the 9–11 month group The sick: carrier ratio during the first year of life was 2:1; after the first year the ratio was 1:4

The comparatively low sick:excretor ratio in the present series can be accounted for partly by the low virulence of some of the serotypes encountered (Table 7) and also by the fact that early treatment of excretors may in some cases have prevented the development of gastro-enteritis.

Solomon and his co-workers [4] emphasise the prevalence of the asymptomatic carrier state in pathogenic E. coli infections and point out the consequent difficulty of incriminating the organism as a causal factor in any single instance of diarrhoea In order to do this, one must demonstrate a significant elevation of serum antibody corresponding to the specific serotype isolated from the faeces This method, however although it has academic value cannot be used as an aid to prompt diagnosis and treatment since the antibodies only appear two to three weeks after infection [6]. Furthermore in the case of babies under the age of nine months the rise of serum antibody is too slight to be of diagnostic value [6]

Rogers et al [3] in a clinical trial of Neomycin in pathogenic E. coli infections found that it was equally effective in the treatment of both symptomless excretors and of cases with symptoms Bacteriological relapse occurred in 18 of their babies. In the present series bacteriological relapse occurred in a higher proportion of symptomless excretors than in babies with gastro-enteritis (Table 5) The reason for this finding remains obscure although treatment was not conducted along the lines of a controlled trial, retrospective study of the treatment of these infants does not reveal any significant differences in dosage or duration of antibiotic treatment or in the proportion of cases in each group in which the organism was sensitive to the antibiotic given (Table 6)

The particular susceptibility to pathogenic E. coli infection of babies with congenital abnormalities of the large intestine has not previously been reported in the literature Swenson [5] cites enterocolitis of either viral or bacterial origin as the most common complication of untreated Hirschsprung's disease but makes no specific reference to pathogenic E. coli infections. Swenson believes that colonic stasis contributes to the seriousness of the the colitis in these cases and accounts for the severe lesions, including ulceration, found in the colon Swenson also describes a severe form of gastro-enteritis which occurs as an early or late complication of recto-sigmoidectomy for Hirschsprung's disease but again does not refer to any specific infecting organism.

In the present series, no case of gastro-enteritis was encountered in untreated Hirschsprung disease In each of the

five babies who became infected a colostomy had been performed. The earliest instance of infection occurred two weeks, the latest five weeks, after colostomy. As has already been said of the seven infected cases of rectal atresia four had had an abdominoperineal pull through operation and three had had a colostomy performed. In six instances infection occurred between the second and fifth post operative weeks in the remaining baby infection occurred more than three months post-operatively. It may be inferred, therefore that colonic stasis was not a pre-disposing cause of infection in our babies and the reason for their increased susceptibility to pathogenic E. coli infection remains speculative. It is possible that the obstructive condition has damaged the bowel wall to an extent that renders it more vulnerable to infection by intestinal pathogens.

Summary

During a 2½ year period 14.6% of 307 infants who had been subjected to surgery in the neo-natal period excreted pathogenic E. coli. Forty-one per cent of the infected infants developed gastro-enteritis, 59% were symptomless excretors. The highest incidence of infection occurred in infants suffering from Hirschsprung's disease and high rectal atresia. Symptomless excretors were more liable to bacteriological relapse after antibiotic treatment than were infants with gastro-enteritis.

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Fetal and Postnatal Development of the Intrarenal Arterial Pattern in Man

A Micro Angiographic and Histologic Study

by ARNE LJUNGQVIST[1]

In a recently published comparative micro-angiographic and histologic investigation on the adult and ageing human kidney it was found that there was a progressive deviation of the intrarenal arterial pattern from that obtaining at the age of 20–30 years—the basic adult pattern [23]. The present investigation is concerned with the arterial system of the fetal and postnatal human kidney studied by the above methods, nd the changes that this undergoes during its development to the basic adult pattern.

Material and Methods

The material consisted of 104 kidneys obtained from 64 autopsy subject from the fourth fetal month up t the age of 20 years (Table 1) In none of the cases was there clinical or histologic evidence of renal disease. Since the clinical information on the length of the pregnancy was in many cases unreliable and any error in this respect is of greater importance in the case of the younger than the older fetuses, an pproximate estimat of the fetal (menstrual) ge was made on the basis of the crown-heel length according to the tables compiled by Patten [28]. None of the fetuses examined was less than 90 mm in length since in such cases attempts to inject contrast medium int the kidneys had proved unsuccessful owing to the small size or advanced post mortem changes.

The arterial tree of the kidneys was filled with 7.5 aqueous suspension of fine barium sulphat (Micropaque). The injection was made into the thoracic aorta (the smaller fetuses) or directly int the renal artery The kidneys were then fixed in 10 % neutral formalin for 4 to 7 days, after which they were imbedded and cut into 150–750 μ blocks frontally from pole to pole These blocks were stereo-micro-angiographed by a method described lsewhere [23]. The blocks then were re-imbedded and cut int 5–6 μ sections, which were stained by the usual histologic methods. From most of the micro-angiographed blocks three such sections were selected for staining From 24 of the micro-angiographed blocks serial sections were cut and stained. These blocks were selected from different kidneys t represent the full age range

Results

The arterial pattern was found to display a gradual development whith ge representative stages of which will be

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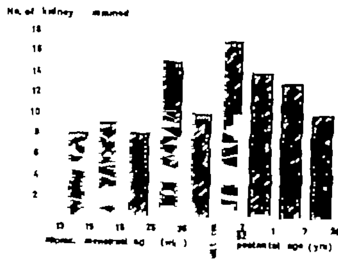


Table 1

described below Since many details in the arterial pattern were qualitively the same at different ages and differed only in quantity a selection of the figures has been made so as to illustrate the details rather than the stage of development of the arterial pattern as a whole

1 *Fetal length 100 mm, menstrual age 13 weeks*

Micro-angiographic findings.—Wide arterial branches entered the hilus of the kidney and ramified in a direction towards the surface of the organ, decreasing progressively in caliber Segments of the branches were curved and ran parallel to the surface of the kidney bearing a resemblance to arcuate arteries. The branches that coursed from the arcuate level towards the surface of the kidney turned back a short distance from the surface towards the arcuate level and terminated in small glomerulus-like capillary tuft (*Fig 1 a*). *Some of the branches* divided into smaller vessels, each of which ended in such a tuft. A number of the tufts consisted of a long, winding vessel (Fig 2 a); others were rounded and composed of single capillary loops which gave the tuft a lobulated appearance (Figs. 1 a and 2 a).

The tufts situated farthest peripherally were separated from the kidney surface by a wide aglomerular zone but which fine twigs were given off by the underlying branches. The wide branches of the hilar region, and the vessels resembling arcuate arteries gave off several long arterioles; these usually had a constriction at their sites of origin (Fig 19) and ran for long distances parallel to the parent artery to terminate in a glomerular tuft. Occasionally an arteriole gave off a new vessel just before *forming its tuft. This new arteriole had the* same appearance as the original one and continued for some distance in the same direction, after which it formed a glomerular tuft (Fig 19) Glomeruli in the hilar and arcuate areas were extraordinarily large and their tufts so dense that the individual capillaries could not be traced From the vascular pole of several of these glomeruli slender twig projected (Fig 5 a) No other types of postglomerular vessels were observed and there were thus no peritubular capillary networks *in the cortex or arteriolae rectae in* the medulla. From their proximal segments some of the long afferent arterioles in the hilar region gave off winding vessels, which ended blindly in the region of the renal pelvis (Fig 6 a)

Histologic findings – There was evidence

of differentiation into a cortical and medullary zone. The primitive medullary pyramids were composed chiefly of connective tissue of the embryonic type containing sparse tubular structures lined with a high cuboidal epithelium having a clear cytoplasm. Beneath the capsule the cortical zone as composed of dense cellular tissue with epithelial cells arranged in rounded or S-shaped structures. Deep in this tissue there were fine vessels filled with contrast medium, these ere identical with the visualized twigs projecting int the aglomerular zone from the underlying arteries. The twigs were either lost in the dense met nephrogenic tissue or led to the rounded cell accumulations or int the S-shaped structures (Fig 3). Deeper in the cortex there were small glomeruli filled with contrast medium. Those seen in the micro-angiograms to consist of winding vessel appeared in the sections t be S-shaped structures, int the lower shank of which the vessel entered and tapered to blind end after following a curved course (Figs. 2b and 4) The vessel was covered by a high cuboidal epithelium. The glomeruli, which were visualized as more spherical and which were composed of capillary loops with lobular arrangement, had the histologic haracteristics of glomeruli with vascular pole and a number of capillary lumina all of which were covered by a lower cuboidal epithelium than in the S-shaped structures (Figs. 1b and Fig 2b) Deeper in the cortex the glomeruli were larger and their capillary tufts denser The glomeruli lose to the medullary pyramids and in the hilar region were still larger and highly vascularized Their afferent arterioles were long and they originated from hilar or arcuat arteries, and their efferent arterioles, which were visualized as short twigs, could not be followed beyond the contrast medium in the serial sections (Fig 5b). The constriction at the sit of origin of an afferent arteriole corresponded to the part of the vessel that passed through the all of the parent artery Large glomeruli filled with contrast medium were found also between the medullary pyramids; they were disposed as paired bands, which extended from the hilar region towards the surface of the kidney Between the bands of each a pair the tissue wa of the same micro-angiographic and hist logic ppearance as that beneath the capsule The intrarenal part of the pelvic cavity was surrounded by embryonic connect ve tissue in which there were a number of w ll developed glomeruli resembling those in the arcuat region (Figs. 6b and 7) These glomeruli which were often djacent to the wall of the renal pelvis, were identical with those seen in the micro-angiograms to be borne by arterioles given off by wide arteries in the hilar region. The winding vessels arising from these arterioles could be followed in the serial sections for some distance int the embryonic connective tissue of the pelvis, in which they ended blindly (Figs. 6b and) None of the glomeruli, whether cortical, juxtamedullary or pelvic, displayed degenerative changes. The tubules in the arcuat and pelvic areas were more highly differentiated than lse where Thus, proximal t bules could be distinguished in these areas, but not in the dense metanephrogenic zone beneath the capsule and between the two glomerular bands of a pair

2 *Fetal length, 150 mm, menstrual age 15 weeks*

Micro-angiographic f ndings.—At this stage a clear differentiation into a cortical and medullary zone was evident in the micro angiograms (Fig 8). The arterial pattern in the cortex was largely similar t that of the foregoing stage However the glomerular zone i the deepest part of the cortex was wider and the paired glomerular bands extending from the pelvic region towards the renal capsule bore a more distinct resemblance to primitive renal columns, with a central aglomerular zone and glomeruli increasing in size towards the corticomedullary junction (Fig 9) Between these renal columns there was a typical medullary vascular pattern, consisting of long, slender arterioles that emerged from long the

cortico-medullary junction and converged on the papilla. In the vicinity of the junction most of these arterioles were so indistinct that it was difficult to ascertain their origin, but those that were discernible could be traced to the vascular pole of the large glomeruli in the juxtamedullary zone (Fig 10) Further peripherally in the cortex no post glomerular vessels were seen, and there was thus no peritubular capillary network. As in the foregoing stage a number of long afferent arterioles were given off by wide branches in the hilar region and their glomeruli were localised in the region of the renal pelvis. From these arterioles vessels also emerged that wound for long distances in the region of the renal pelvis and anastomosed with one another

Histologic findings—The cortico-medullary junction was more distinct than in the foregoing stage and the zone of visualized glomeruli was wider There was a zone of metanephrogenic tissue centrally in the renal columns and beneath the capsule The glomeruli in the pelvic connective tissue were large well developed and filled with contrast medium, and near them there were lumina lined with epithelium and suggestive of proximal convolutions. From the serial sections it was evident that each of these tubules emerged from an adjacent glomerulus. The winding vessels given off by the afferent arterioles in the region of the renal pelvi ramified only in the pelvic connective tissue The arteriolae rectae visualized in the micro-angiograms were narrow and had thin walls None of the glomeruli seen displayed degenerative alterations

3 *Fetal length 220 mm menstrual age 18 weeks*

Micro-angiographic findings—At this stage a greater number of interlobular arteries were given off by the arcuate arteries, to run parallel into the cortex and give rise to short afferent arterioles. Their glomeruli were smaller and less mature in appearance the closer they were to the renal capsule and to the central line of a renal column (Fig 10)

Nor at this stage was there any peritubular capillary network in the cortex. The interlobular arteries gave off slender twigs into the aglomerular zone beneath the capsule and along the centre of a renal column (Fig. 10). In the juxtamedullary zone the glomeruli were large were composed of numerous capillaries and gave off efferent vessels, which ramified into arteriolae rectae leading into the medulla. The juxtamedullary glomeruli situated on the medullary side of the arcuate arteries belonged to very long afferent arterioles, which ran parallel to the arteries. The arterioles could be traced to the arcuate arteries themselves or to interlobar arteries or afferent arterioles in the region of the renal pelvis. Such a vessel given off by arcuate and interlobar arteries often had a constriction at its site of origin (Fig. 1?). Glomeruli were numerous in the renal pelvis (Fig 11) From some of their afferent arterioles vessels were given off to form an anastomosing network in the pelvic region (Fig 12) Some segments of these vessels showed a tendency for spiralling (Fig 13). The arteriolae rectae of the medulla were wider than in the previous stage and consisted of branches of efferent arterioles from the juxtamedullary glomeruli and from glomeruli localised in the region of the renal pelvis. The latter arterioles followed an ascending course along the adjacent calyceal recess, before curving over this to divide into arteriolae rectae which passed into the medulla (Fig 14) Other efferent arterioles of pelvic glomeruli ramified only in the region of the renal pelvis.

Histologic findings—The histologic picture did not differ essentially from that of the previous stage and the vessels bore the same relationship to the other structures. There were no signs of degenerative alterations.

4 *Fetal length 310 mm menstrual age 25 weeks*

Micro-angiographic findings—At this stage some of the glomeruli of the pelvic region were incompletely visualized and con-

sisted of a few fine capillaries. Their pre- and postglomerular vessels were however apparently normal and the latter coursed over the calyceal recess and into the medulla as arteriolae rectae (Fig. 15 a), or ramified in the pelvic area. Similar partially visualized glomeruli with normal afferent and efferent arterioles and arteriolae rectae were also seen on the medullary side of the arcuat arteries. Most of the arteriolae rectae however derived from apparently normal juxtamedullary glomeruli (Fig 16). Only in the juxtamedullary and pelvic regions were there postglomerular vessels. N glomeruli were seen in zone beneath the renal capsule or along the central line of the renal columns.

Histologic findings.—This was the earliest stage in which degenerative changes were observed. The glomeruli that were incompletely visualized in the pelvic region and along the arcuat arteries displayed focal sclerosis of the tuft and fibrosis of the capsule (Fig 15 b). Both the afferent and the efferent arterioles of such a glomerulus were w ll filled and normal in ppearance Tubules near these glomeruli showed evidence of atrophy Most of the glomeruli in the connective tissue of the pelvis and along the arcuat arteries were, however intact. Apart from the degenerative changes mentioned the histologic picture did not differ essentially from those of the earlier stages.

5 *Fetal length, 450 mm, menstrual age 38 weeks*

Micro-angiographic find ngs.—At this stage efferent arterioles were seen t emerge not only from the juxtamedullary and pelvic glomeruli but also from the glomeruli situated further out in the cortex (Fig 17) The efferent arterioles of the latter glomeruli ramified after a short course t form an anastomosing network of fine capillaries, hich resembled the peritubular capillary network of the mature kidney (F g 18). The aglomerular zone beneath the renal capsule and along the midline of the renal columns was much narrower than in the foregoing stages. The constriction of an afferent arteriole t its site of origin was often very distinct (Fig 19) Some arterioles in the pelvic region and on the medullary side of the arcuat arteries ramified to form arteriolae rectae that led to the medulla without first forming glomerular tufts (Figs. 20 and 22 a) Other arterioles in these areas bore a partially visualized glomerulus but most of the glomeruli were normal. The glomerular zone on the cortical side of the arcuate arteries cont ined few extremely slender vessels, these were given off by interlobular arteries or fferent arterioles and, after a short distance each of them terminated as a blind stump or as a few very fine twigs.

Histologic findings.—In the greater part of the cortex the glomeruli were large and contained numerous capillaries The metanephrogenic zone with primitive glomeruli beneath the capsule and centrally in the renal columns was narrow In the pelvic connective tissue and in that on the medullary side of the arcuat arteries there were intact glomeruli and a number that were partly or wholly fibrosed. The afferent arteriole of such a completely degenerated glomerulus coursed into, or tangential t the glomerular scar and then continued directly into the efferent arteriole with no change n calibre (Figs. 22 b and). This vessel divided int arteriolae rectae Such wa the nature of the aglomerular arterioles forming arteriola rectae which were visualized in the pelvic region nd along the arcuat arteries. From the afferent segment of such pelvic arterioles vessels were given off t the connective tissue of the renal pelvis. Some of the fferent segments did not pass over the calyceal recess and into the medulla but instead turned int the pelvic connective tissue in which they ramified. The visualized blindly ending vessels situated on the cortical side of the arcuat arteries led t glomerul that displayed partial or complete degeneration; these were situated in otherwise intact tissue composed of well developed nephrons (Fig 21). The partially degenerated glomeruli contained few capillary

loops filled with contrast medium, while the other loops were sclerosed, there was pericapsular fibrosis. No efferent arterioles, or fragments of such were observed near these glomeruli

6 *Full-term fetus*

Micro-angiographic findings.—In these kidneys glomeruli were observed far out beneath the renal capsule and in the central part of the renal columns Here however *the glomeruli were smaller and more primitive* in appearance than deeper in the cortex. In addition there were glomerular and aglomerular arterioles resembling those in the previous stage

Histologic findings.—Only a few obviously primitive S-shaped epithelial structures were observed in the metanephrogenic zone Both intact and degenerated glomeruli were found in the connective tissue of the renal pelvis and in that along the arcuate arteries. Many of the completely degenerated ones could be recognized as fragments of glomeruli only in serial sections. Cortically to the arcuate level there were also scarred glomeruli. Many of these were minute and they were apparently not approached by arterioles, whereas to others a fine afferent arteriole could be followed to its termination at the vascular pole No efferent arterioles were seen to emerge from these glomeruli.

7 *Postnatal pattern*

Primitive glomeruli were rarely found in the periphery of the cortex of kidneys from full-term subjects more than one week old.

The degenerative changes observed in the fetal kidneys were modified further after birth. For instance no glomeruli were visualised in the pelvic region after about 6 months of age and from 7 years no definite glomerular remains could be identified in the now *fairly dense connective tissue of* the pelvis. Thus, the vessels emerging from the pelvic region and passing over the calyceal recess were all aglomerular

At all ages both intact and degenerated glomeruli were observed in the perivascular connective tissue of the arcuate arteries. The degenerated glomeruli were traversed or touched by the corresponding arterioles, the efferent segments of which split up into arteriolae rectae leading to the medulla. Whether the relative number of degenerated and intact glomeruli with this localisation varied with age was difficult to decide However an increasing number of the visualized aglomerular arterioles had no apparent glomerular scar along their course in the periarcuate connective tissue

At all ages *there were small glomerular scars* in the otherwise normal cortical tissue They were found both immediately cortically to the arcuate level and further peripherally in the cortex. Either such scar was associated with an atrophic afferent arteriole or it bore no evident relationship to a vessel These scars varied widely in number even among kidneys of the same age so that no evaluation of the frequency of these glomeruli with age was possible

From the age of about 7 years an occasional arteriole—glomerular unit was seen in the juxtamedullary zone the afferent arteriole of which emerged from the proximal segment of an interlobular artery or from an arcuate artery and formed a continuous vessel with the efferent arteriole through the scarred glomerulus (Figs. 23 *a* and *b*). These glomerular scars were situated not within but outside the periarcuate connective tissue where they were surrounded by tubules. The efferent segment divided into arteriolae rectae which led to the medulla.

Discussion

It is evident from the results of this study that not only is the development of the intrarenal arterial pattern progressive but that it is also modified by regressive changes. This fact seems not to have been noted *before* though Sandberg [30] and Kampmeier [14 15] showed that regressive changes of nephrons are a normal feature in the fetal kidney

The youngest kidneys of the series—

menstrual age 13 weeks—contained a number of glomeruli with well developed capillary tufts. The present investigation thus throws no light on the histogenesis of the first metanephrogenic glomeruli. The presence of well-developed afferent arterioles and glomerular tufts at the fourth fetal month suggests that even at this early stage some degree of glomerular function is anatomically possible. This bears out the view that the kidney begins to function early in fetal life [8, 16], and that glomerular filtration occurs as early as the third month [24].

It is well known that maturation of glomeruli proceeds from the juxtamedullary zone outwards to the periphery of the cortex, and that during the development of the kidney the most primitive glomeruli are found beneath the capsule and along the central line of the renal columns, while the largest and most mature ones are found in the juxtamedullary zone [13, 25]. This pattern of glomerular development was evident also in the present material. In those kidneys in which most of the glomeruli situated in the periphery of the cortex were of a primitive histologic appearance this zone was seen in the micro-angiograms to be aglomerular. The renal columns then appeared as aglomerular paths bordered by arteriole glomerular units, a feature that has been described as being typical of the immature kidney [1, 26].

The maturation of the glomerulus in man has been thoroughl[illegible] [illegible]xamined by MacDonald & Emery [25] but they did not examine the vascularization in the various stages of development. Using an injection technique on kidneys of laboratory animals Lewis [20] examined the vascular pattern of the glomerulus at different stages of maturity but as he used only the clearing method he did not ascertain which histologic stages of maturity were represented by the various types of capillary tufts. According to the still most widely held view on the vascularization of the renal corpuscle a vascular twig given off by an interlobular artery ramifies to form a capillary tuft which invaginates the proximal end of a primitive tubule [1, 9]. However the validity of this theory was questioned as early as 1909—by Huber [13]—and the findings in a number of recent studies suggest that the glomerular capillaries are formed *in situ* in this end of the tubule [8, 17]. It was found in the present study that where the appearance of the metanephrogenic blastema was so primitive that no glomerular pre-stages could be identified on histologic grounds, small vascular processes from the underlying more mature cortical tissue terminate[illegible] in the primitive blastema, often clo[illegible] round accumulations of epithelial [illegible] It is likely therefore that such a[illegible] lations represented, among other [illegible] tures, primitive glomeruli. The [illegible] mitive form of glomerulus th[illegible] Donald & Emery identified [illegible] n S-shaped structure rese[illegible] bule. Huber [13] demonstra[illegible] lower curve of such a struc[illegible] [illegible] rular pre-stage and that [illegible] structure will give rise to [illegible] tubules. It has been [illegible] that such a pro-glomer[illegible] insofar a[illegible] a fine vas[illegible] from the underlying [illegible] passes into the lo[illegible] [illegible] haped structure [illegible]

blindly MacDonald & Emery's stage 2 is represented by a crescentic Bowman capsule enclosing glomerular capillaries. A glomerulus having this histologic appearance was seen in the micro-angiogram as a solitary winding vessel. Primitive glomeruli of similar appearance were described by Lewis [20], who following the development of the individual glomerular capillaries during the subsequent maturization of the glomerulus, claimed to have resolved the vascular pattern of the mature glomerulus. The absence of any histologic check of the extent of the filling of the injection specimens dictates the need for reserve in assessing Lewis's results. It cannot be excluded, for instance that the small number of glomerular capillaries which enabled the course of individual ones to be traced was due to incomplete filling of the tufts. For in the present study it was found that the glomerular capillary system, after the stage of a winding vessel, became first more rounded and then gradually larger and more highly vascularized, and that the glomeruli of these more highly developed stages, which histologic examination proved to be completely filled with contrast medium, were so densely vascularized in the micro-angiograms that the individual capillaries could not be followed. This study thus does not contribute much to our knowledge of the vascular pattern of the mature glomerulus. Nor does it clear up the problem of whether the proximal end of the tubule is invaginated by an approaching vessel or whether in this end of the tubule vascular lumina are formed that then fuse with the afferent arteriole. On the other hand, it has been found that a glomerulus is not formed through invagination of the proximal end of a tubule by a capillary tuft but that, when this end of the tubule has formed a recess, the future glomerulus contains only a fine, curved vessel. This gradually develops into a glomerular tuft with simultaneous differentiation of the recess into a Bowman capsule.

In kidneys that were so young that there were still primitive glomeruli in the periphery of the cortex, glomeruli with degenerative alterations were also found. Such glomeruli were observed at the seventh fetal month, after which they appeared to increase in number. In the youngest of these fetuses degenerated glomeruli were found in the connective tissue of the renal pelvis and in that around the arcuate arteries. From the ninth fetal month degenerated glomeruli were found also in other parts of the cortex.

The presence of degenerated glomeruli in the neonatal kidney has long been recognized [11]. Emery & MacDonald [5], who have made a close study of this congenital glomerulosclerosis found that degenerated glomeruli were most numerous towards the end of fetal life and during the first two post-natal years. Prior to partus most degenerated glomeruli were located in the juxtamedullary zone, while post partum they were more numerous in other parts of the cortex. Sclerosis of one or more capillary loops and thickening of the parietal layer of the Bowman capsule were regarded as histologic characteristics. Some glomeruli were completely fibrosed. Similar changes were displayed by the degeneratively altered glomeruli on the cortical side of

the arcuate level in the kidneys of the present material and they resembled those that Lennartz & Rudolph [19] classed as developmental anomalies of the glomerular tuft. It would thus seem as if glomerulosclerosis of the type described is a completely normal feature but its cause remains obscure It appears not to be due to primary abnormality of the glomerular tuft as Lennartz & Rudolph suggested, since in the present series such glomeruli were not found until the later fetal months and since when partly degenerated, the glomerulus displayed filling of both an afferent arteriole and intact capillary loops. The fact that these glomeruli were situated in otherwise sound tissue with no signs of degenerative changes in the tubules, would suggest however that they had either never been associated with tubules or had lost their former association with them, and that they had therefore degenerated.

The degeneratively changed glomeruli found in the pelvic and periarcuate connective tissue were obviously quite different in type from those discussed above They were distinctly visible in the fetal kidney and increasingly so the younger the subject, down to the seventh fetal month when they were first seen. At the higher post natal ages, on the other hand, it was found that glomerular fragments, although not seen in the histologic sections, must be incorporated in the connective tissue, since this contained aglomerular arterioles such as result from glomerular degeneration. Incorporation of degenerated glomeruli in the periarcuate connective tissue may ccount for the reduction in the number of degenerated juxtamedullary glomeruli with gr re ported by Emery & MacDonald [5]. A typical feature of the pelvic and periarcuate glomeruli was that when they degenerated a direct continuity was established between the afferent and efferent arterioles through the glomerular scar Aglomerular vessels then were seen to curve over the calyceal recesses or run along the medullary side of the arcuate arteries, before turning into the medulla as bundles of arteriolae rectae Similar aglomerular arterioles have previously been observed by Gänsslen [7] who referred to them as "Begleitgefässe by Baker [9] who found them to emerge from the vascular plexus of the renal pelvis and supply only the papillae and by Hammersen & Staubesand [10] who found them to build a vascular plexus around the arcuate arteries as intralobar continuations of the plexus of the renal pelvis. None of these authors performed histologic examinations of the injection specimens and they were therefore unaware of the relationship between these vessels and the glomeruli and hence of their formation nd true nature It has been shown in the present study that all the pelvic and periarcuate arterioles that in the micro-angiograms appeared to be aglomerular and formed arteriolae rectae verae leading to the medulla consisted of arteriole-glomerular unit the glomeruli of which had degenerated. It was evident moreover that vessels of the renal pelvis were derived from the arteriole-glomerular units present in the region, and not the reverse as Baker thought to be the case Damage to the pelvic vascular network therefore need not affect the supply of the medulla by the pelvi rteriole-glomerular units.

In kidneys from the beginning of the fourth fetal month the only postglomerular vessels to be seen were short twigs emerging from large juxtamedullary glomeruli a few weeks later there was a medullary supply consisting of arteriolae rectae which were ramifications of these postglomerular juxtamedullary vessels. There seems to have been no previous investigation of the development of the vascular supply of the medulla most studies of the medullary supply having been concerned with whether there are aglomerular pathways (so-called arteriolae rectae verae) as well as glomerular ones (so-called arteriolae rectae spuriae) to the medulla of the fully developed kidney In an earlier study it was demonstrated that the adult human kidney contains both aglomerular and glomerular vessels to the medulla and that the former increase in number with age at the expense of the latter [23]. The aglomerular pathways proved to be formed through the establishment of direct contact between the afferent and efferent arterioles via degenerated juxtamedullary glomeruli. The present study as shown that arteriolae rectae of the medulla develop from efferent juxtamedullary and pelvic arterioles from the fourth fetal month, and that from the seventh an increasing number of these vessels begin to change to arteriolae rectae verae through degeneration of the glomeruli of the respective units. From the seventh year of life there is also another type of arteriolae rectae verae namely those the degenerated glomeruli of which are situated in the juxtamedullary zone outside the periarcuate connective tissue It has been demonstrated that arteriolae rectae verae of this type increase in number with age [23] and in essential hypertensio[n] [22], and that they also appear in pyelon[e]phritically altered tissue [18].

Constriction at the site of origin of th[e] afferent arterioles was observed at [all] ages in the present series a It was [like] that of the adult and ageing huma[n] kidney [23]. Such constrictions have bee[n] observed by others on corrosion specimen[s] and interpreted as a pressure regulatin[g] mechanism [3 27]. In the study on th[e] adult and ageing human kidney it wa[s] pointed out however that the possibl[e] functional importance of these constric[-] tions could not be assessed on injectio[n] specimens since it could not be exclude[d] that they were artefacts, the part of th[e] arteriole passing through the wall of th[e] parent vessel offering greater resistanc[e] to the injection pressure than the rest o[f] the arteriole The same argument applie[s] to the present study which thus throw[s] no further light on the possible signifi[-] cance of the constrictions.

To judge from the present findings n[o] postglomerular cortical vessels develop until after the eighth fetal month. On the basis of an investigation on the rabbit fetus Lewis [-1] considered that the post glomerular cortical vessels develop from a sinusoidal system, which exists at a very early stage of fetal life To judge from his description and illustrations this sinusoidal system is identical with the whole intertubular space in that it gives, as it were a negative picture of the tubular pattern It would seem as if Lewis s sinusoidal filling might be an arte[-] fact resulting from rupture of vessels dur[-] ing the injection, a possibility that he does not mention but that cannot be ruled out, since no histologic check of the kidneys

and the extent to which vessels were filled was performed It is true that the apparent absence of postglomerular vessels in the cortex of the present specimens throughout the greater part of fetal life may also have been an artefact due to the contrast medium penetrating into but not through, the glomerular tufts but this is unlikely in view of the fact that as early as the fourth fetal month there was filling of the postglomerular vessels in the juxtamedullary zone and of their fine ramifications into the medulla Nor were any cortical efferent arterioles evident in the histologic sections of these kidneys Moreover it has been shown by reconstruction of serial sections that the efferent arterioles in the human kidney do not begin to form until the afferent vessels nd their glomeruli are fully developed [4]. The present study has shown that up to the last fetal month the circulation through the renal lobes probably is mainly medullary and takes place through the juxtamedullary and pelvic arteriole-glomerular units and arteriolae rectae and that not until after this age a cortical circulation is also anatomically possible In addition up to the seventh fetal month the lobar circulation is entirely glomerular and after this age both aglomerular nd glomerular paths are available

Summary

The development of the intrarenal arterial pattern in man has been studied by parallel micro-angiographic and histologic examinations on 104 kidneys obtained from 64 autopsy subjects ranging in age from the fourth fetal month to the twentieth year of life Various stages of development of the glomerular capillary tuft were noted but the most primitive ones were no longer observed after the first week of life

In the fourth fetal month well-developed arteriole-glomerular units were found in the juxtamedullary zone and the pelvic connective tissue These subsequently gave off postglomerular vessels to the medulla From the end of the fourth fetal month a cortico-medullary vascular pattern was present with arteriolae rectae leading to the medulla and a cortical arrangement of the glomeruli. Postglomerular vessels in the cortex did not appear until after the eighth fetal month, and up to that time the lobar circulation is therefore probably medullary

Glomeruli in the pelvic and periarcuate connective tissue began to degenerate during the seventh fetal month, with the formation of so-called arteriolae rectae verae to the medulla through canalization of the glomerular scars. These scars were gradually incorporated into the connective tissue and became histologically unidentifiable

From the seventh year of life juxtamedullary glomeruli outside the periarcuate connective tissue began to degenerate with the formation of arteriolae rectae verae. Vessels to the renal pelvis were given off by pelvic arteriole-glomerular units.

From the ninth fetal month there was evidence of congenital glomerulosclerosis—that is sclerosis of scattered cortical glomeruli with atrophy of the whole arteriole-glomerular unit

Fig. 11 Micro-angiogram of the hilar and pelvic region in fetal kidney (menstrual age 15 weeks). A number of arteriole-glomerular units are given off by the large arteries of the area. × 45.

Fig 12. Micro-angiogram of the pelvic region in fetal kidney (menstrual age 17 weeks), showing pel ic rteriole-glomerular units. From one of the afferent arterioles vessel is given off (arrow) that follow a winding course in the pelvic region and anastomoses with branches of another vessel coming from above 90

Fig 13. Micro-angiogram of another part of the pelvic region in the same kidney as in Fig. 12. From an afferent arteriole a pelvic branch is given off (arrow), which, for short distance, follows spiral course (top) 90.

Fig. 14 a. Micro-angiogram from a full term newborn showing pelvic glomerulus (smaller arrow) adjacent to wide interlobar artery The efferent arteriole curves over the calyceal recess (larger arrow) and ramifies int a bundle of arteriolae rectae which descend into the medulla. 45. b. Histologic section from the tissue in Fig 14 a. *Below* segment of the interlobar artery filled with contrast medium. *Above right* the well developed glomerulus is seen t be situated in the pelvic connective tissue with few tubules nearby The efferent rteriole leads out of the picture (arrow) Verhoeff vanGieson G 225.

Fig 15 a. Micro-angiogram from a full term newborn showing a pelvic arteriole, which ascends along the calyceal recess. It gives off one branch which has glomerulus-like structure (*smaller rrow*) and which curves over the recess int the medulla *arteriolae rectae*; the main arteriole continues in its original direction (*larger arrow*) and subsequently becomes *Begleitgefäss* in the cortico-medullary junction. 45. b Histologic section from the tissue at the smaller arrow in Fig 15 a. The branch that curves over the calyceal recess is seen t pass tangentially to degenerated, partly filled glomerulus in the calyceal connective tissue van Gieson. 225.

Fig 16. Micro-angiogram from fetal kidney (menstrual age 38 weeks) showing part of renal lobe with a wide glomerular zone in the cortex and medullary arteriolae rectae emerging from the juxtamedullary glomeruli. The glomeruli become smaller the further peripherally they are situated. 45.

Fig. 17 Micro-angiogram from a fetal kidney (menstrual age 38 weeks) showing glomeruli also far peripherally in the cortex and arteriolae rectae emerging from large juxtamedullary glomeruli. Visualization of post-glomerular cortical capillaries is particularly clear in the top left area. 45.

Fig. 18. Micro-angiogram from full-term newborn showing a cortical arteriole glomerular unit with a wide afferent (*larger arrow*) and thinner efferent arteriole (*smaller arrow*) The latter splits up into peritubular capillaries. 150

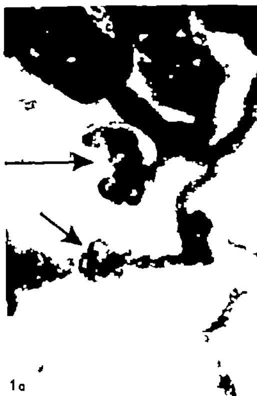
Fig 19 Micro-angiogram of the juxtamedullary zone in fetal kidney (menstrual age 30 weeks) showing long afferent arterioles which course along the medullary side of an arcuate artery and form ll developed glomerular tufts. The postglomerular vessels are very eakly visualized (*top right*) owing to poor filling. One of the afferent arterioles is constricted at its site of origin at the arcuate artery (arrow). 90

Fig 20 Micro-angiogram of calyx region from an infant (age 12 months) showing an aglomerular arteriole with the same course as that in Fig. 15. In this case the branch turning over the calyceal recess was found t pass through completely scarred glomerulus. The segment of the vessel along the calyceal wall displays marked spiralling 45.

Fig 21 Histologic section from renal cortex of an infant (age 12 months) showing degeneratively ltered glomerulus with trophic afferent arteriole (arrow), thickened capsule and sclerotic obliteration of a number of peripheral capillary loops. The tubules adjacent t the glomerulus are intact van Gieson. 600

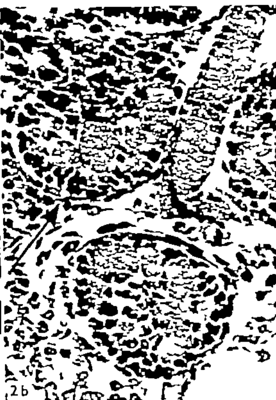
Fig. 22 a. Micro-angiogram from a kidney of bild (age, 7 years) showing sectioned arcuate artery and arteriole (arrow), passing through the whole thickness of the section (750 μ). 90 b. Histologic section of the tissue at the arrow in Fig. 22 The arteriole passes through degenerated glomerulus in the periarcuate connective tissue (arrow). *Top left* segment of the arcuate artery is seen. 225. High-power view of the degenerated glomerulus in Fig. 22 b. The arteriole passes tangentially to the scarred glomerulus, the capsule of which is sclerotically thickened and the capillary loops partly hyalinized. van Gieson. 450.

Fig. 23 a. Micro-angiogram from a kidney of child (age, 7 years) showing an aglomerular juxtamedullary arteriole (arrow) which ramifies into arteriolae rectae leading to the medulla. 90


1a


1b
1c


2a


2b







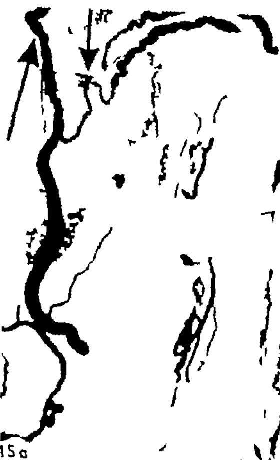


6a

6b

6c

7


15a


15b





8

19

21


22 a


22 b


22 c



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From the Department of Pediatrics, Sharon Hospital and the Rogoff Medical Research Institute of the Department of Experimental Biology Tel Aviv University and Kupat Holim, Beilinson Medical Center Petah Tikva Israel

Use of Fluoxymesterone in the Treatment of Growth Retardation

by ZVI LARON

Growth retardation is one of the most frequent complaints for which children are referred to a pediatric endocrine clinic [14].

The available amounts of human growth hormone are scant [6] and therefore its clinical use is limited to selected patients. Furthermore growth hormone seems effective only in children lacking this hormone [11]. The clinician is therefore often compelled to make use of other substances with growth-promoting properties. The most potent drug with such a quality is testosterone However this hormone has been found to stimulate skeletal maturation more than linear height [13] and also causes virilizing effect in children. In recent years analogues of testosterone have been synthetized with the aim to maintain or increase the anabolic properties and at the same time diminish the androgenic ones One of these compounds is 9 alpha fluoro-11 beta-hydroxy 17 alpha methyltestosterone synthetized by Herr *et al.* [2] This substance later called fluoxymesterone was found to have 20 times the myotrophic activity and 9.5 times the androgenic activity of methyltestosterone [7] Although this substance has been frequently used in the treatment of mammary carcinoma [4 8] or as an anabolic drug [9] only few reports on its effectiveness in growth retardation are available [5 10 1?].

Following our own personal experience with the short term treatment of growth retardation with fluoxymesterone [5] we performed a study in children with growth retardation administering fluoxymesterone for a period of six months.

Subjects and Method

Fifty three children of both sexes suff[illegible]ng from growth retardation were st[illegible]died They were divided into two groups ( ) those without secondary sex[illegible] signs, 21 children (Table 1), and (b) children show[illegible]g signs of puberty at the beginning of the period of treatment 32 children (Table 2) The age of the children at the beginning of the observation period ranged from 3 years 9 months to 14 years 8 months. Only children with retarded bone age were included in this study. Many of the children were also underweight for height. The children studied comprised three children with hypopituitarism (Pts. Nos 5, 18 22) t[illegible] children with primordial dwarfism (Pt N[illegible] 18 [illegible] Bloom syndrome

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TABLE 1 *Weight and height increment before during and after*

Er = penile erections; P.E. = enlargement of penis; C.E. = enlargement of clitoris; P.H. = pubic hair

Subjects					Pretreatment control period			
No.	Sex	Age, years	Weight kg	Height cm	Months, no.	Mean wt increment g/mo	Mean ht. increment cm/mo.	Initial dose mg/kg/d
1	M	8 /7	24	117	3	168	0.23	[illegible]
2	F	3 /12	11	67.5	4	50	0.04	[illegible]
3	M	9	21	119	3	70	0.30	[illegible]
4	M	6 /12	18.5	114	3	0	0.70	0.11
5	F	6 /12	16.7	99.5	3	150	0.29	0.11
6	M	6 10/12	15.8	106	4½	310	0.11	0.11
7	M	4 /12	11	91.5	7	143	0.25	0.12
8	M	2 /12	14 4	89	7	200	0.31	0.13
9	M	4 /12	13	91	18	144	0.21	0.13
10	F	4 11/	15.5	98	7	−29	0 40	0.13
11	M	5 /12	14.3	104.1	5	140	0.60	0.13
12	M	5 /12	14	97.8	2	0	0 60	0.14
13	F	3 /1	11 7	83.5	14	167	0.45	0.14
14	F	4 10/12	14	96	8	−25	0.34	0.14
15	M	4 /12	12.8	96	4	−100	0.40	0.15
16	M	9	24	120.5	7	2‥8	0.41	0.16
17	M	5	17.8	95 7	6	22	0 26	0.16
18	F	5 /12	7 9	73	5	90	0 30	0.17
19	F	9 /12	22.7	115.7	12	380	0 31	0.18
20	M	5 /12	18.7	101.5	4	400	0.18	0.18
21	M	3 /12	11 4	89	4	275	0 60	[illegible]
22	M	7 /	9.3	78.3	5	84	0.12	[illegible]
23	M	5 /12	13.2	97 4	6	123	0.31	[illegible]
24	M	3 /12	10.6	90.7	5	140	0.55	[illegible]

[3] and one of the idiopathic type (Pt no 48) one patient with gonadal dysgenesis (No. 19) and 3 children with chondrodystrophy (Pts. N 8, 9 and 13)

The children were weighed and measured and subjected to a complete physical examination, including measurement f genitalia, at least every three months. Children up to 90 cm body height were measured in a recumbent position. If over 90 cm the standing body height was registered. At the beginning of the study weight and height changes were followed in all children for several months without medication Children who became ill during this period were excluded from the study

Fluoxymesterone (Halotestin, Upjohn) was administered by mouth daily in one or two divided doses. Treatment was continued for 6 to 7 months and after discontinuation of fluoxymesterone the weight and height changes could further be f llowed for several months in 42 out of 53 children. Three children of group "a" and one child in group "b received two courses of treatment (they are identified by roman numerals)

X-rays of the wrist were performed at the beginning of the study before and after fluoxymesterone treatment and after the post-treatment control period Bone age was estimated according to the standard of Greulich & Pyle [1]

Results

The pertinent information concerning the children studied and the influence of fluoxymesterone (Halotestin) on body weight and height are summarized for the prepuberal children in Table 1 and for

fluoxymesterone (halotestin) treatment in prepuberal children

A.B.A.=advancement of bone age more than expected. Grading: ± slight; ? = questionable

	Halotestin			Post-treatment control period		
Mths, no.	Mean wt. increment g/mo.	Mean ht. increment cm/mo.	Side-effects	Months, no	Mean wt increment g mo	Mean ht increment, cm/mo.
[illegible]	0	0.41		7	223	0.41
[illegible]	200	0.86		13	61	0.35
6	200	0.61		4	250	0.30
6	350	0.61		5	100	0.41
[illegible]	[illegible]	0.60		5	80	0.64
3	220	0.74		17	11_	0.43
[illegible]	200	0.63		6	133	0.31
[illegible]	334	0.70		6	33	[illegible]
[illegible]	150	0.80		3	420	0.10
[illegible]	233	0.80		10	180	0.53
[illegible]	250	0.63	Er?	5	60	0.30
[illegible]	220	0.75		3	80	0.20
[illegible]	160	0.53		3	350	0.60
[illegible]	303	0.43		7	57	0.45
[illegible]	320	0.62		4	360	0.70
[illegible]	450	0.63	P.F A.B.A.	3	66	0.2_
6	417	0.83	P.E. ±	3	200	0.45
6	300	0.60	C.E. ±	—	—	—
[illegible]	480	0.63	C.E. ? A.B.A.	3	−100	0.20
7	235	1.10	Er A.B.A.	—	—	—
[illegible]	316	0.55	Er A.B.A.	—	—	—
[illegible]	230	0.53	P.E	—	—	—
[illegible]	333	0.90	P.H. ?	5	80	0.13
5	192	0.61	P.E.	—	—	—

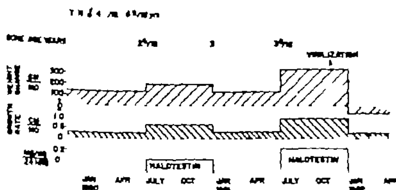


Fig. 1 Mean body weight changes, mean growth rates and skeletal maturation in prepuberal boy with growth retardation before during and after treatment with fluoxymesterone (Halotestin).

TABLE 2 *Weight and height increment before during and after*

Er = penile erections; P.E. = enlargement of penis; C.E. = enlargement of clitoris; P.H. = pubic hair

Subjects					Pretreatment control period			
No.	Sex	Age years	Weight kg	Height cm	Months, no.	Mean wt. increment g/mo.	Mean ht. increment, cm/mo.	Initial dose mg/kg day
5	F	1 /	21..	139.3	4	75	0.61	[illegible]
26	M	1 /	24	138.6	8	224	0.30	[illegible]
27	F	9 /12	20.5	130	10	140	0.40	[illegible]
28	F	13 /12	41.1	142.7	9	800	0.26	[illegible]
29	F	7 /12	13.5	103	3	−160	0.06	0.11
30	M	14 /12	34	146	6	50	0.18	0.11
31	M	13 /12	34.5	136	11	182	0.42	0.11
32	M	8 /12	20	118	11	234	0.36	[illegible]
33	M	13 /	35	138.8	10	120	0.47	0.11
34	F	11 /12	23	131.4	13	305	0.44	0.11
35	M	14 10/12	[illegible]	141	8	445	0.51	0.11
36	M	13 /12	31	139.7	9	590	[illegible]	0.11
37	M	14	33.0	138.5	8	150	0.30	0.11
38	M	14	[illegible]	142	3	400	0.32	0.11
39	M	12 /12	30.3	137.5	12	[illegible]	0.44	[illegible]
40	M	9 /12	20.5	130	19	187	0.33	[illegible]
41	F	8 /	22	113.4	11	590	0.41	[illegible]
42	M	14 /12	42	144	4½	310	0.76	0.27
43	M	13 /	28.8	131.8	4	300	0.90	[illegible]
44	F	11 /	20.3	128	9	278	0.67	[illegible]
45	M	10 /12	23	140	11	226	[illegible]	[illegible]
46	M	13 /12	27.4	130	8	260	0.38	0.17
47	F	13 /12	36.6	144.6	6	−16	0.30	[illegible]
48	F	10 /12	14.	100.7	15	170	0.26	[illegible]
49	F	10 /	20	150.6	10	180	0.61	[illegible]
50	M	13 /	38.3	141	11	417	0.32	[illegible]
51	F	10 /12	24	132.6	4	225	0.32	[illegible]
52	M	11	23.5	132.5	11	45	0.33	[illegible]
53	F	11 /	[illegible]	[illegible]	5	200	[illegible]	[illegible]
54	M	13 /12	37.9	140	7	−43	0.39	[illegible]
55	M	10 10/12	26.8	[illegible]	18	120	0.36	[illegible]
56	F	10	20	113	9	0	0.32	0.21
3	M	14 /12	30.1	133.7	8	175	0.33	0.21

the puberal children in Table 2. The patients are listed according to the size of the daily dose of fluoxymesterone expressed as mg per kg body weight at the beginning of the treatment. In all but two patients (Nos. 1 and 20) fluoxymesterone induced a marked gain in body weight. After discontinuation of treatment out of 46 children followed, 12 continued to gain weight at a rate similar to that in the treatment period, 23 continued to gain weight at a decreased rate and 11 lost weight. The response in body height was as follows, with the exception of three prepuberal (Pts. Nos 2, 4 and 1) and 4 puberal children (Pts. Nos. 25 29 35 and 4.) all children showed an increment in their linear growth rate upon treatment. The children receiving high doses of the drug usually showed a better growth response. Upon discontinuation of treatment the linear growth rate decreased in all but

fluoxymesterone (halotestin) treatment in puberal children.

A.B.A. advancement of bone age, more than expected. Grading: ± slight ? = questionable

Halotestin			Post-treatment control period		
Mean wt. increment, g/mo.	Mean ht. increment cm/mo	Side-effects	Months, no.	Mean wt increment, g/mo	Mean ht increment, cm/mo.
835	0.43		6	−16	0.27
465	0.85		6	83	0.43
415	0.67		6	330	0.84
960	0.35	A.B.A.	3	700	0.10
200	0.50		3	122	0.30
600	0.66			950	1.20
1000	0.88	P.E., A.B.A.	3	500	0.86
272	0.60	P.H.± A.B.A.	—		—
1600	0.90		—	—	—
545	0.80		3	1200	0.84
385	0.42		3	430	0.50
770	1.10	A.B.A.	3	430	0.90
850	0.95	P.E.	5	80	0.83
870	0.76		—	—	—
1150	0.75		3	330	1.10
300	0.53		2	350	1.00
385	0.90	C.E.? A.B.A.	6	400	0.66
1800	0.60		3	0	0.40
700	0.83			800	0.70
870	0.83	A.B.A.	5	20	0.42
415	0.73	P.E.	3	200	0.70
450	0.48	P.E.±	2	100	0.70
1000	0.25	A.B.A.	3	−160	0.10
167	0.30		3	−33	0.31
450	0.80	A.B.A.	3	366	0.50
280	0.67	A.B.A.	2	880	0.40
800	0.90	C.E.±	3	200	0.80
615	1.00	P.E., A.B.A.	3	130	0.80
543	0.63		—	—	—
880	0.72	P.E., A.B.A.	—	—	—
1010	0.80	A.B.A.	3	390	0.60
880	0.97		4	320	0.61
830	0.81	P.E.	—	—	—

four adolescent children. However in most of these children the growth rate, though less than during the treatment period, remained for several months higher than it was before institution of therapy.

Comparing the overall mean response to fluoxymesterone in prepuberal and puberal children, (mean dose in group "a" was 0.145±0.028 mg/kg/day and in group "b" 0.156±0.034 mg/kg/day) it is evident that the puberal children (group "b") showed a better response to body weight gain (monthly mean 690±315 g vs 280±g in group "a") whereas the mean height increment during treatment was similar in both groups (group "a" 0.67±0.15 cm and group "b" 0.67±0.29 cm per month).

Side-effects such as erections, enlargement of the penis or clitoris, and/or maturation of skeletal bones more than expected for the period of treatment oc

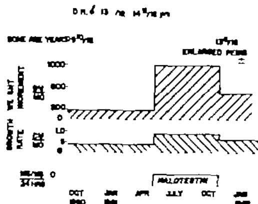


Fig. 2. Mean body weight changes, mean growth rates and skeletal maturation in puberal boy with growth retardation before during and after treatment with fluoxymesterone (Halotestin).

curred in prepuberal children treated with a daily dose of fluoxymesterone of over 1.5 mg/kg body weight The dose effect in a child of this group is graphically illustrated in Fig 1 In the puberal children virilizing effects and advancement of bone age was observed already with doses over 0 1 mg per kg body weight per day *The response to treatment in one of these* children is illustrated in Fig 2. In none of the children was enlargement of the breasts observed and in the older girls menstruation was not disturbed by fluoxymesterone

Discussion

Similar to our previously published experience [5] clinical studies have been made by Reilly & Gordan [1*] and Mellman *et al.* [10] Reilly & Gordan studied 16 patients aged 9 years or more. Treatment periods ranged from 6 to 41 months with a mean of 16 months. The authors concluded that although virilizing effects occurred they were not bothersome to the patients. There was no evident stimulation of bone maturation greater than that of linear height. Body weight was not registered, precluding the calculation of a dose weight response Mellman *et al.* studied six children without growth and skeletal retardation and 10 children with growth retardation. In eight children virilizing effects were noted and in six bone age advanced more than height age. In this report, too the body height dose ratio could not be recalculated.

Our findings do not agree with those of Reilly & Gordan that fluoxymesterone does not affect bone maturation and, on the other hand, we cannot fully agree with *Mellman et al. that fluoxymesterone* generally stimulated skeletal maturation more than linear growth and that it offers no significant advantage over methyltestosterone Our experience in the past using a 3-month treatment period [5] and the present study using 6–7 month treatment periods, showed beneficial effects of fluoxymesterone on both body weight and height. The occurrence of virilizing side effects and increased stimulation of skeletal maturation was correlated with the dose per body weight time ratio. Whereas over a three-month period a dose of 0.25 mg/kg body weight/day was required to cause virilizing side-effects, the virilizing dose decreased to 1.5 mg/kg/day *in prepuberal children and 0 1 mg/kg/day* in puberal children, when extending treatment to 6 months. Smaller non virilizing doses were still effective in stimulating linear height and body weight gain.

Knowing that with advancement of puberty as a result of secretion of endogenous sex hormones, bone age if retarded sometimes matures faster than at a normal rate we are not sure as to how much of the advancement of bone age noted in the

puberal children was due to fluoxymesterone and how much was due to the endogenous hormones. Participation of endogenous hormones could also explain why puberal children showed a better response to body weight gain.

The question arises whether prolongation of treatment to several years would require in order to prevent side-effects, a reduction in dose to such a level that it would cease to be beneficial as a growth stimulant. We still do not know whether the undesirable side-effects can be avoided by intermittent treatment, and years will pass until we shall know as to whether it will be possible to influence ultimate height by treatment with an anabolic substance

Summary

Fluoxymesterone (9 alpha fluoro-11 beta hydroxy 17 alpha methyltestosterone) was administered for 6 months to *1 prepuberal and 3_ puberal children suffering from growth retardation. Four children received two courses of treatment Fluoxymesterone induced a gain in body weight in all but two children and stimulated linear growth rate in all but seven children. In prepuberal children with a daily dose of over 0 15 mg/kg body weight signs of virilization and/or increased stimulation of skeletal maturation were observed, in puberal children the virilizing dose was 0 10 mg/kg.

Ackn wledgement

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Studies on Human Lactation

I Effect of Dietary Protein and Fat Supplementation on Protein Fat and Essential Aminoacid Contents of Breast Milk

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A positive relation between dietary and milk composition with regard to protein and fat was inferred from the cross-sectional studies reported in a previous communication [10]. It was argued that if such a relation exists we should obtain favourable effects on milk levels of these constituents with dietary supplementation. Longitudinal studies were therefore carried out on changes in the fat protein, and essential amino-acid composition of milk following dietary supplementation.

Material and Methods

Subjects of poor nutritional status were chosen for the investigations as the hypothesized relation was found only within certain ranges of dietary intake.

The supplementation was carried out mainly with regard to fat and protein, but in either case in order to investigate how the results of such supplementation are affected by improvement of the diet with regard to the other constituents, additional supplements were made in some of the experimental groups. In other words, some of the fat supplementation groups were given additional protein and vice versa. The effects of additional vitamin supplementation were also studied. The chief constituent supplemented was started at small doses, whereas additional supplements were given at some dosage level throughout the experiment. The results obtained were compared with those of isocaloric groups. Studies were also made of the effects of such supplementation on the 24 hour yield of milk. The results of these investigations are recorded in this paper.

Subjects. The sixty subjects used in this study were all between the first and third month of lactation and belonged to families with a monthly per capita income below Rs. 10 ($2). Their mean dietary intake at the commencement of the experiment was determined by actual analyses of the whole day diet of the subject by making collections of the matched amounts of all the foodstuff consumed by the subject including snacks, beverages, and dietary supplement if any. The diet was so analysed for three consecutive days. The composition of the diet was found to be as follows:

Calories	1300
Fat	18.3 g
Protein	21.0 g
Carbohydrate	270 g
Ascorbic acid	1.5 mg
Thiamine	0.23 mg
Riboflavin	0.18 mg
Pantothenic acid	2.2 mg

[1] Officer of the Scientists Pool of the Council of Scientific & Industrial Research

Nicotinic acid	2.4 mg
Cyanocobalamin	0.26 mcg
Biotin	0 03 mg
Pyridoxine	0.35 mg
Folic acid	0.30 mg

Supplementation procedure In the first part of the experiment fat and protein supplementation were started at initially low levels and increased progressively to levels beyond which dietary increases were found from the previous study [10] to have no effects on milk levels. The additional supplements were made at constant levels and again their size was determined so as t raise dietary intake to the minimum level corresponding to ceiling levels in milk on the basis of the previous study Nine groups of five subjects each were used, four for the different fat supplementation treatments, four for the different protein supplementation treatments, and one, as a control group receiving no supplementation Each dosage level was maintained for a month before change to the next level was made, according to the data shown in Table 1. Five such levels were used.

Two additional groups receiving fat and protein supplementation were compared with those receiving carbohydrate supplementation in the form of glucose at isocaloric levels. A *control group received no supplementation*. The supplementation was done at two different levels for each group. Protein was supplemented in the form of skimmed milk powder t 20 and 40 g and fat in the form of butter at 20 and 35 g

Milk yield was determined by weighing the infant before and after each feed over a 24 hour period for three consecutive days (and nights) The 4 hour milk intake as *taken as the total yield of milk*.

Collection / milk. The samples, made up of equal aliquots from both breasts, ere collected on three consecutive days in sterilized test tubes by manual expression, and brought t the laboratory in thermos flasks packed with ice.

The effects of diurnal variations were sought to be minimized by collecting the

TABLE 1 *The design of the experiment*

Chief constituent supplement	Dosage level, g: 1st	2nd	3rd (months)	4th	5th	Group[a]	Additional supplements[b]
I. Fat (in the form f butter)	5	15	_5	35	45	1	None.
							15 g protein.
						3	Standard dose of vitamins
						4	15 g protein + standard dose of vitamins.
II Protein (in the form of skimmed milk powder)	10	20	20	35	40	5	None
						6	Standard dose of vitamins.
						7	20 g fat.
						8	Standard dose of vitamins + 20 g fat.
III. None (control group)						9	

Each group consisted of 5 subjects

[b] Protein and fat were supplemented so as t raise daily dietary intake t 40 g and 43 g respectively Vitamins were supplemented in the form of multivitamin tablets (Dumex compan) at 1 tablet a day

samples at specified time for all the subjects. The variation in composition between right and left breasts was sought to be controlled by taking equal aliquot from both breasts and that between fore and after milk, by taking the foremilk in all cases, the subjects having been requested not t nurse the infants for at least 2 hours before collection.

The analysis of milk was done at the end of each supplementation period prior to the introduction of the next dosage level.

Methods of chemical analyses

Milk. The fat content of the milk was estimated by the method of Chiba *et al.* [4].

The nitrogen content of the milk was estimated by microkjeldahl method. The value obtained was multiplied by 6.38 and taken as the protein content of milk.

For estimating the essential aminoacids, an alkaline hydrolysat was prepared for the estimation of tryptophan, and an acid hydrolysate for that of others. The circular paper chromatography technique described by Gothoskar *et al.* [6] was used for the estimation of tryptophane. The microbiological assay technique described by Barton Wright [2] was used for the others.

Food. Fat and protein content of the diet are estimated as described lsewhere [10]. The procedure for the estimation of the aminoacids is the same as that for milk. The dried homogenates of the diet were used for the preparation of acid and alkaline hydrolysates. The rest of the constituents of the diet were estimated by the method of Banerjee & Biswas [1].

Results

The changes in the fat and protein contents f milk with the progress of fat supplementation are shown in Table * from hich it can be seen that th fat content increases with th dose supplemented to a ceiling level of 33 g per day which corresponds to a total intake f 50–55 g of fat per day when we take into account the initial intake of the subjects. No such increase is found in the control group. The increase in the fat content is found to be of the same order in all the four groups supplemented suggesting that the fat content of milk is not influenced by additional supplementation of protein and vitamins Rather the additional protein supplementation is found to have a small beneficial effect on protein content.

Similar results are obtained with regard to protein supplementation as can be seen from Table 3 The increase in dietary protein is found to be associated with an increase in milk levels up to a dose of 35 g per day which corresponds to a dietary intake of 53–58 g of protein per day further increases having no effect. Here again additional supplementation with regard to fat and vitamins is found to have no effect on protein levels but the former is seen to be associated with increases in fat content

As might be expected, increase in the protein content of milk is seen to be associated with a general increase in aminoacid content the increase being statistically significant with regard to histidine methionine and tryptophan. As th increase in the case of these three aminoacids is of the same order in all the four protein supplementation groups, the combined mean values for these amino-acids t different level of protein supplementation are shown in Table 4 The significant relation with regard t histidine is interesting in the light of the suggestion that this amino-acid is essential for infants though not for adults [3]. The values are found to reach ceiling val es t the same time as milk protein.

TABLE 2 *Variation in the fat and protein contents[a] of milk with increasing fat supplementation*

The number of subjects five in each group. F denotes fat content of milk and P denotes protein.

Fat supplement[b] per day g	Supplementation groups: Fat		Fat + protein		Fat + vitamin		Fat + protein + vitamin		Control group (No supplementation)	
	F	P	F	P	F	P	F	P	F	P
0	3.78	1.00	3.86	0.95	3.83	1.11	3.75	1.09	[illegible]	[illegible]
5	4.15	1.06	4.25	1.08	4.15	0.93	4.10	1.13	3.00	[illegible]
15	4.35	0.96	4.75	1.13	4.40	0.98	4.85	1.15	3.80	[illegible]
25	4.61	0.99	4.90	1.11	4.88	0.98	4.95	1.13	3.65	[illegible]
35	4.80	0.98	5.00	1.06	4. 0	0.97	5.00	1.14	3.00	[illegible]
45	4.71	0.94	5.00	1.09	4.65	0.96	5.03	1.1	3.80	0.77

[a] Expressed in terms of g/100 ml.
[b] The initial protein intake before supplementation in the subjects was 18 t 23 g per day Each level was maintained for a month.

It may be argued that the effects of protein and fat supplementation on the respective constituents in milk may be due to an increased calorie intake However the results of additional supplementation with regard to fat and protein appear to negate this possibility Nevertheless additional confirmation in this regard was sought to be obtained b comparing the effects of protein and fa supplementation with those of carbohydrate supplementation at isocaloric levels The results are presented in Tables 5 and 6 from which it would again appea that the increases are specific to the constituent supplemented

TABLE 3 *Variation in the protein and fat contents[a] of milk with increasing protein supplementation*

The number of subjects was five in each group P denotes protein content of milk and F denotes fat

Protein supplement[b] per day g	Supplementation groups: Protein		Protein + vitamin		Protein + fat		Protein + vitamin + fat		Control group (No supplementation)	
	P	F	P	F	P	F	P	F	P	F
0	0.92	3.90	0.94	4.01	1.06	3.70	1.02	3.85	1.08	[illegible]
10	1.08	3.75	1.07	4.00	1.18	4.29	1.10	4.05	1.08	[illegible]
20	1.18	3.90	1.16	3.93	1.20	4.30	1.22	4.05	0.96	[illegible]
30	1.27	3.80	1.25	4.03	1.29	4.30	1.29	4.13	0.99	[illegible]
35	1.32	3.85	1.31	4.00	1.33	4.20	1.34	4.16	0.9	[illegible]
40	1.34	3.85	1.33	4.00	1.35	4.18	1.38	4.20	0.94	[illegible]

[a] Expressed in terms of g/100 ml.
[b] The initial protein intake before supplementation in the subject was 18 to 23 g per da Each level was maintained for month

TABLE 4 *Histidine methionine and tryptophan[a] contents of milk with protein supplementation.*

The number of subjects was fiv in each group.

Protein supplement per da g	Histidine		Methionine		Tryptophan	
	Supple-mentation	Control	Supple mentation	Control	Supple-mentation	Control
0	32	31	16	16	10	9
10	35	29	18	16	12	9
20	37	30	20	16	13	9
30	38	29	21	16	15	9
35	38	30	1	16	15	9
40	39	30	22	16	18	9

[a] Expressed in terms of mg/100 ml.
[b] The initial protein intake before supplementation in the ubjects was 18 t 23 g per day Each level of supplementation was maintained for month.

The results of dietary supplementation on the 4 hour yield of milk are presented in Table 7 from which it can be seen that neither protein nor fat supplementation has any effect on milk yield at the doses and periods of treatments used It should be pointed out that the results are based on a moderate dietary improvement with regard to only one constituent, viz., fat or protein. We cannot rule out the possi bility that beneficial results might have been obtained with an over-all improvement in the diet in the face of the obser vation that the yields reported for Indian subjects are generally low as compared to those reported by Western investiga tors.

TABLE 5. *Comparative values for the protein content of milk (g %) with protein and carbohydrate suppleme tatio*

The number of subject was five in each group

Protein[a] supple-mentation group	Isocaloric group receiving glucose	Control group (X supple-mentation)
0.99	0.99	0.93
±0.06	±0.09	±0.08
1.20	0.99	0.94
±0.10	±0.10	±0.07
1.21	0.98	0.94
±0.12	±0.08	±0.09

The supplementation was done at two levels, protein at 20 and 40 g and fat, at 20 and 35 g da and brought total in akes to levels of 88 and 53 per day respectivel

TABLE 6 *Comparat ve val s for the fat content of milk (g) with fat and carbohydrate supplementation*

The number of subjects as five in each group.

Fat supple ment tion group	Isocaloric group receiving glucose	Control group (X supple mentation)
3.80	3.75	3.65
±0.16	±0.1	±0.15
4.40	3.90	3.70
±0.20	±0.18	±0.18
4.76	3.90	3.70
±0.21	±0.18	±0.19

The supplementation was done at wo levels, protein at 20 and 40 g and f t, at 20 and 35 g/da and brought total intakes levels of 88 and 85 g per da respecti ely

TABLE 7 *Effect of dietary supplementation on 24-hour yield[a] of milk.*

The values given are means with standard errors. The number of subject was five in each group

Experimental group	24 hour yield of milk[a] Dosage levels[b]		
	0	I	II
Fat supplementation group	605 ±16	595 ±16	590 ±16
Protein supplementation group	570 ±13	585 ±13	595 ±15
Control group (no supplementation)	560 ±12	550 ±12	545 ±13

[a] Expressed in terms of ml.
[b] The supplementation was done at two levels, protein as 20 and 40 g, and fat, at 20 and 35 g/day and brought total intakes to levels of 58 and 55 g/day respectively

Group 7 Fat		Group – Protein	
Initial	Final	Initial	Final
2.50	4.00	0.97	1.09
3 75	4.00	0.98	1.12
3.25	4.00	0.87	1.01
4.00	4.50	0.92	1.12
4.00	4.25	1 01	1.11

Discussion

Thus the results of these studies confirm our previous hypothesis [10] regarding the existence of a positive relation between dietary and milk levels of fat and protein within certain ranges of dietary intake. It is of interest to note that the levels of dietary intake corresponding to ceiling levels of milk are in agreement with those inferred from the studies reported earlier [10].

It will be seen that the additional supplementation, particularly with regard to protein, is associated with relatively small increases in milk levels. This is not surprising in view of the small dose supplemented and the fact that the subjects had *undergone the stresses of pregnancy* and lactation on a woefully inadequate diet. Even so the results were found to be quite consistent in that all the subjects showed some improvement in milk levels. Some typical sets of values are given below:

It would appear from the data of Tables 2 and 3 that ceiling levels of milk with regard to fat and protein are attained at a dietary intake of 50–55 g in either case In this connection, Gopalan [8] has suggested that the minimum dietary intake supporting ceiling levels in milk may serve as a possible criterion of maternal requirement. From this point of view a diet containing 50–55 g each of fat and protein plus 270 g of carbohydrate and yielding 1750 to 1800 calories should constitute the minimum requirement in lactation. It is seen that these levels are far below the recommended allowances for lactating women. However what is minimal level for the maintenance of lactation may not be the optimal level from the point of view of maternal health. Even so it is to be noted the values arrived at call *for* almost a 200% increase in fat and protein intake.

A comparison is made in Table 8 of the available nutrients in 24 hour milk with reported infant requirements at a body weight of about 5 kg It can be seen that the requirements are not met even at this stage. When it is recalled that the infants were fully breastfed beyond the sixth month when their body *weight* should have been of the order of 7 kg according to standard norms, or *at least* about 6 kg according to the data reported for poor class Indian infants by Gopalan

TABLE 8 *Data[a] on nutrients in 24-hour milk in comparison with recommended allowances*

Constituent	Before supplement ation[b]	After supplement tion	Recommended allowances at 5 kg body weight [9]
Fat, g	23	29	
Lactose g	42	42	70?
Protein, g	6.0	8.2	10
Calories	400	460	875
Leucine mg	435	482	770
Isoleucine, mg	432	454	650
Valine mg	318	336	525
Histidine, mg	186	222	115
Lysine, mg	422	486	5_5
Phenylalanine mg	240	264	450
Threonine, mg	270	288	300
Methionine mg	96	120	160
Tryptophan, mg	87	84	110

[a] Estimated on the basis of 600 ml of milk yield.
[b] Protein supplementation was carried out for 5 months with progressively increasing doses. The details are given in Table 1.

[7], the degree of inadequacy is seen to be much greater

It will be seen from a comparison of the availability of essential amino-acids on a percentage basis (Table 9) that the quality of proteins in the milk secreted is poor with regard to leucine valine, phenyl alanine methionine tryptophan but shows improvement on supplementation, particularly with regard to methionine and tryptophan. Thus supplementation with good quality protein may have a beneficial effect not only on the content of protein in milk but also on its composition with regard to essential amino-acids.

Our present finding that carbohydrate intake at iso-caloric level has no effect on fat content is at variance with that of Polonovski [11] who found an increase in

TABLE 9 *Percentage composition of essential amino-acids in breast milk as compared with recommended norms*

Amino-acid	Before supplement ation[a]	After supplement ation	On the basis of recommended allowances [9]
Leucine	17.8	1 .3	31.6
Isoleucine	1 4	1 .1	16.6
Valine	12.9	12.6	14.7
Histidine	7.5	8.3	3 2
Lysine	17 4	17 1	14.7
Phenylalanine	9.5	10 0	12.6
Threonine	10.9	10.8	8 4
Methionine	3.9	4.5	4 7
Tryptophan	..4	3.1	3.0

[a] Protein supplementation was carried out for 5 months with progressively increasing doses. The details are given in Table 1

fat content with the addition of 100 g of glucose daily to the diet Although a small increase in milk fat content with glucose supplementation was obtained in our subjects the increase was not found to be statistically significant and was less than 15 of the increase in the fat supplementation group. However there may be differences in the initial nutritional status of our subjects and those of Polonovski particularly the carbohydrate/fat ratio of the diet which may perhaps affect the results obtained.

In conclusion, the trend of the investigations outlined has been to suggest that within certain ranges of dietary intake there is a positive relation between dietary and milk constitution of fat protein and essential amino-acids. This observation underscores the possibility that, even when lactation is maintained on an inadequate diet the quality of the milk secreted may suffer as a result with detriment to the requirements of infant nutrition and points out the need for dietary

improvement during lactation from the stand point of both maternal and infant welfare

Summary

Longitudinal studies were carried out in subjects of poor nutritional status on changes in the fat protein and essential amino-acid composition and 24-hour yield of milk following dietary supplementation. The supplementation was carried out with regard to fat and protein singly and in combination, and with and without added vitamins. The results obtained were compared with those of an isocaloric group supplemented with equivalent amounts of carbohydrate.

The supplementation studies showed that fat and protein contents of milk increase to a ceiling level with the dose supplemented till dietary levels of 50-55 g are reached in regard to either The increase in protein content was found to be associated with a general increase in essential amino-acids, the same being significant with regard to histidine methionine and tryptophan.

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Hyperbilirubinaemia in Full Term Newborn Infants

A Follow Up Study

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The indications for exchange transfusion in full-term newborn infants with hyperbilirubinaemia not due to Rh immunization are still under discussion [1–9]. We have previously reported a group of full term infants with hyperbilirubinaemia during the first days of life, half of them treated by exchange transfusion [6]. The report included a comparison of the two groups with regard to clinical and laboratory findings in the neonatal period at 5–8 weeks, and at 3–4 months of age.

The present paper deals with a follow up investigation of these infants performed at the age of 24 to 32 months.

Material

The series comprised 94 full term infant born at the University Hospital in Uppsala during 1957 and 1958, in whom the serum bilirubin concentration was 20 mg/100 ml or more. Of these infant 46 were treated by exchange transfusion and 48 were left untreated as controls. Among the untreated, three showed a peak bilirubin value of 25 mg/100 ml or more (23.0, 27.2 and 27.2 mg/100 ml respectively). Four of the treated showed peak bilirubin concentrations of 23 mg/100 ml or more immediately before the transfusion (25.5, 25.8, 23.6 and 26.0 mg/100 ml respectively). In 21 infants ABO blood group incompatibility was present, but signs of a haemolytic process were found in only six infants, three of them belonging to the untreated and three to the treated group. Of the last mentioned three infants two required repeat exchange transfusion and before the second transfusion their bilirubin levels reached 31.5 and 26.4 mg/100 ml respectively.

Of the untreated infants 47 were available for follow-up investigation. One infant had died of capillary bronchitis at the age of 3 months; at necropsy there were no signs of kernicterus or brain damage. All the 46 treated infants were examined.

The untreated infants were examined at an average age of 26.8 months (range 24–32) and the treated infants at 26.7 months (range 24–31).

At follow-up examination a detailed case history was taken from the mother with special regard to the occurrence of behaviour abnormalities, symptoms of impaired hearing and vision, and possible deviations in motor development and performance, as well as illness. Information about the child's physical and mental development included the age at head-lifting, sitting, crawling, standing, walking without support, climbing stairs, and talking. Both general physical and special neurological examinations were performed. Audiometry and intelligence tests were not used. The examinations were done by us personally except in four children who were examined by other paediatricians.

Results

At the follow up investigation definite neurological abnormalities were demonstrated in one boy who belonged to the treated group and who had had a maximum bilirubin concentration of 23 mg/100 ml He showed muscular hypotonia of the lower limbs with absence of deep tendon reflexes, but no signs of ataxia or athetosis. His elder brother who had showed similar symptoms at the same age has now at the age of 17 years a typical peroneal muscle atrophy of the Charcot-Marie-Tooth type. It seems most probable although it is not yet proved, that our patient suffers from the same disease

Otherwise none of the children, treated or untreated, showed any gross neurological abnormalities such as spasticity hypotonicity paresis, athetosis ataxia, nystagmus, blindness, or deafness There was no case of microcephalus or hydrocephalus.

Some minor abnormalities, however were noted in both groups. In the untreated group two children had had typical breath holding attacks (initial peak bilirubin concentration 22.2 and 23.8 mg/100 ml respectively) one child (22.0 mg/100 ml) had a slight divergent strabismus and one child (20 0 mg/100 ml) had a skull circumference of 53 cm at 27 months of age a value exceeding the normal maximum (M+2SD) by 1 cm. In the treated group one child (23 0 mg/100 ml) had had two breath holding attacks, two children (21 4 and 23.5 mg/100 ml respectively) had had simple initial convulsions; one child of this group (21 4 mg/100 ml) had a slight divergent strabismus and a head circumference of 54 cm at the age of 25 months (– cm above the normal limit) and another child (24.6 mg/100 ml) had a head circumference of 53 cm at the age of 25 months.

Motor development appeared normal in all children, and no obvious signs of mental retardation or behaviour disorder were observed in any case.

One girl deserves special attention for two reasons She had early hypothyroidism and showed some neurological abnormalities 1½ years after the follow-up examination presented in this paper She had a slowly rising bilirubinaemia during the neonatal period, the peak bilirubin value of 22.5 mg/100 ml was reached on the 8th day when an exchange transfusion was performed. Subsequently the serum bilirubin slowly decreased, but normal values were not recorded until 2½ months after birth. At the age of 7 weeks the diagnosis of hypothyroidism was established The follow up examination at 30 months of age did not disclose any neurological abnormalities or mental retardation The child has been examined regularly because of the hypothyroidism and at 4 years of age she was found to have a disturbance of coordination with minor athetoid movements and slight ataxia and possible mental retardation.

Two rather uncommon *complications connected with the technical procedures* were noted. In one case a heel infection with osteitis appeared in the neonatal period, probably the result of the puncture for blood *sampling At follow-up examination* this heel was still slightly larger than the other In the other child, in whom the exchange transfusion had to be performed via the right *femoral vein, swelling of the* right leg was observed after the transfusion, but disappeared within one week. At the age of 13 months, when the patient started to walk, the mother noted swelling of the right leg especially after exercise This tendency was still present at

the time of follow-up examination, but was less pronounced. The circumference of the right calf was 1 cm larger than that of the left, but otherwise no difference was noted between the two legs.

Comments

In this series the criterion for hyperbilirubinaemia was a total serum bilirubin concentration of [illegible]0 mg/100 ml or more. Alternate infants were subjected to exchange transfusion as soon as possible after this level was reached, and those not thus treated were used as controls. Since the serum bilirubin concentration fell spontaneously in most untreated infants shortly after the serum bilirubin had passed 20 mg/100 ml there was no significant difference between the two groups with regard to the degree of hyperbilirubinaemia. The hyperbilirubinaemia persisted for a longer time in the untreated group however and the mean bilirubin value of this groups was consistently higher during the first two weeks of life [6].

The first two follow up investigations which were performed at 6–8 weeks and 3 months of age did not reveal any difference between the untreated and the treated infants with regard to neurological abnormalities and development: all seemed normal. The difficulties in assessing deviations from the normal at this early age are obvious. The whole series was therefore subjected to a third follow-up examination at the age of [illegible] t [illegible] ½ years, when it is easier to evaluate possible signs of disease as well as physical and mental development. The study revealed some abnormalities in both groups. It does not seem likely that any of these findings may be attributed to brain damage of the type induced by hyperbilirubinaemia. The girl with hypothyroidism however showed a minor disturbance in coordination which despite repeated examinations was not found until 4 years of age and which is not known to be a typical finding in congenital hypothyroidism. She never had excessive hyperbilirubinaemia and the question remains of whether her disturbance in coordination was caused by the hyperbilirubinaemia and if so whether the hypothyroidism made her more susceptible to the toxic effect of bilirubinaemia.

In the previous paper [6] we concluded that a serum bilirubin level of 20 mg/100 ml was most probably not critical with regard to brain damage in full term non erythroblastotic infants with hyperbilirubinaemia. Nor was it possible to fix any other bilirubin concentration as a criterion for exchange transfusion. As we have previously stated, it seems reasonable to restrict exchange transfusion to those few full term, non-erythroblastotic infants who show excessive hyperbilirubinaemia (>25 mg/100 ml)

Summary

A follow up study is presented of [illegible] full term infants with neonatal hyperbilirubinaemia, 46 of which were treated by exchange transfusion. At examination between [illegible] and [illegible] ½ years of age no differences with regard to neurological abnormalities or development could be demonstrated between the two groups. No definite signs of kernicterus were present in any case. One child with congenital hypothyroidism showed a minor disturbance in coordination not apparent until the age of 4 years

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Venous Pressure in the First Hour of Life and Its Relationship to Placental Transfusion

by W JEGIER,[1] W BLANKENSHIP and J LIND

Introduction

A major and significant hemodynamic event at or immediately after birth is the transfer of blood from the placenta into the newborn organism. The problem has evoked interest in investigators for many decades. The first important contribution came from Haselhorst [12] who mad a direct recording of intravascular pressure in the umbilical vessels. In another of his publications [13] he reported on weight changes of the neonate in the immediate postnatal period. He estimated a net weight gain of 70 g in the first three minutes of life and attributed it to the placental transfusion. Hörmann *et al.* [15] arrived at a similar figure of 70 ml of blood as an average amount of placental transfusion transferred from the placenta to the infant de Marsh *et al* [1] expressed blood from the placentas of infants with early and late clamped umbilical cords and found an average difference in the content of blood to be 48 ml. Gunther [11] and Duckman [7] estimated the amount of blood transferred from the placent to the baby by continuous recording of the weight of the newborn. The latter emphasized the role of gravity in the process of placental transfusion. Whipple *et al* [37] estimated the mount of placental transfusion enhanced by manually milking the cord to be 22 % of the existing blood volume He denied the fact that merely the delay in severing the umbilical cord will result in a significant volume of blood transferred From recent data obtained by Usher Shepard & Lind [32] it ppears that the volume of placental transfusion lies in the vicinity of 60 of the existing blood volume i.e. approximately 160 ml of blood for an average infant of 3500 g The estimation of the extent of placental transfusion thus varies from 20 to 60 % of the existing blood volume If the problem were magnified into dult dimensions the amount of transferred blood would correspond to 1500 to 3000 ml of blood poured into a compensated circulatory system within a period of seconds or minutes.

Animal xperiments [10 35] are in

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agreement that the immediate effect of large amounts of fluid transferred rapidly into the circulation is an increase in venous pressure. This effect is transitory and there is evidence that peripheral capillaries and venoules may act as reservoirs.

Sharpey-Shafer [28] was able to demonstrate in human experiments the hemodynamic effect of rapid intravascular infusion of fluids using sodium chloride serum serum concentrate and blood. The volume of infused fluid varied from 1500 to 2000 ml at a rate of 54 to 108 ml/min. The majority of his human volunteers showed a short lived elevation of venous pressure measured in the antecubital vein not exceeding 11 cm of water and lasting from 15 to 20 minutes following the completion of the infusion. One patient, receiving 1500 ml of blood at a rate of 60 ml /min showed an elevation of pressure lasting 50 min. Chest radiograms demonstrated an exaggerated prominence of the superior vena cava shadow and an increase in number and density of the pulmonary markings.

Purpose of the Study

Our primary objective was to study the effect of placental transfusion on the hemodynamics of the newborn infant as reflected in the venous pressure. We undertook to register venous pressure distal and proximal to the ductus venosus, i.e. the pressure in the umbilical recess and the inferior vena cava or the right atrium. Recordings of central venous pressure in the first hour of life and interrelation of electrical acoustical and mechanical events will be reported separately.

Methods and Materials

Twenty four normal newborns were studied. The infants were delivered vaginally with birth weights ranging from 2680 to 4700 g. The gestational periods varied from 38 to 41 weeks. All pregnancies were uneventful, except one case which was complicated by mild toxemia of the mother (systemic blood pressure 160/120 during delivery). No medication was given to the mothers during parturition with the exception of the toxemic mother. This particular infant was extracted by suction cup.

The infants were delivered in bed and placed at the level of the mother's back. They were divided into three groups according to the mode of handling of their umbilical cords.

Group I consisted of seven infants who had their cords "milked" manually for 3 minutes following delivery. The cord was clamped after the last of the ten stripping movements was completed.

Group II consisted of eleven infants with cords clamped immediately following delivery of the baby. In five cases the cord was clamped before the first cry of the infant, in the remaining six cases the clamping occurred simultaneously with the first breath.

Group III included six infants with delayed clamping of the umbilical cord after all visible pulsations had disappeared, i.e. usually within 3 to 5 min after delivery of the infant.

The study was conducted with the infant placed on a padded board and kept warm and comfortable by use of a heat lamp and rubber nipples. As soon as it was feasible a polyethylene catheter with an internal diameter of 1.15 mm was introduced under sterile conditions into the umbilical vein and manipulated 12 to 15 cm from the cutaneous ring, i.e. until the recording of a free pulsatile venous pressure was obtained. A blood sample was then withdrawn for hematocrit and to insure that the catheter tip was placed in a venous channel and had not slipped into the left atrium. One lead electro-

cardiogram and a precordial phonocardiogram was recorded simultaneously. After a satisfactory recording of all the event had been obtained the catheter was withdrawn under continuous recording of electrically integrated mean pressure t a distance of 4 to 7 cm from the skin ring, a "peripheral venous pressure presumed t be that f the umbilical recess was recorded in this posi tion. In eight cases it was found impossible to advance the catheter into the "central" position and thus pressure recordings were made in the peripheral position only.

The position of the catheter was confirmed by the measurement of distance under fluoroscopic control in two stillborn infants who were then dissected and the measure ments confirmed. With the catheter introduced 10 and 12 cm from the skin ring respec tively the tip was placed in the lower right atrium. In one of the cadavers the catheter was advanced to a distance of 13.5 cm from the skin ring and the superior vena cava entered. The radioopaque catheter that was used for the determination is significantly stiffer than the polyethylene tube used in the study and therefore the distances invol ved in the cadaver may be shorter than in the living infant.

The polyethylene catheter was connected to an Elema-Schönander pressure transd cer with a pressure range of 0 to 300 mm Hg. The strain gauge was then attached t a preamplifier system. The damping of the system was regulated by the use of ppropriat filters (in the majority of cases filter I was used). The natural frequency of the system was 70 cps. The pressure curves were recorded on a direct writing, Elema Mingograph four channel recording unit. The paper speed used for the majority of tracings as 100 mm/sec permitting an easier evaluation of the records.

A saline-filled pol ethylene tube was in serted through the nostril int the esophagu 15 to 17 cm from the nares of the infants. The free end of tubing was connected to an identical pressure recording system as described for the enous pressure recordings.

The reference point for the pressure determination was set at the level of the sternal angle. This point in space does not correspond to the level of the right atrium and thus the recorded pressures may be slightly higher than the true right atrial pressure. The difference in recorded pressure with the zero point at the sternal angle and the mid-axillary line was 1.5 to 2 mm Hg. Lyons *et al.* [18] reviewing the problem of the reference point suggest t place the zero level in a constant reference to the table, as all measurement referring to the thorax will vary with the size of the subject.

Blood samples were collected in heparinized syringes and after careful mixing were transferred t capillary tubes and were cen trifuged at 11500 rpm for 5 min. The hema tocrit values were read from the Guest Reading Chart [9]. N correction for trapped plasma was introduced.

Results

The plotting of the values recorded in a central and peripheral position against the hematocrit resulted in the graphs of Figs. 1 and 2. The pressure calculated in mm Hg is an electrically integrated mean pressure recorded with the infant relaxed and brea thing quietly as indicated by the phonocardiogram and the intraesophageal pressure pattern. Care was taken to include only pressures showing good respiratory fluctuations thus ascertaining that the catheter lumen was free of obstruction. The peripheral and central pressures were not recorded simultaneously. They were read on a pull back tracing -15 seconds part. One pressure tracing was read at a 40 second interval and in one case the recording was interrupted and the time between the values could not be deter mined.

The work of Usher Shepard & Lind [32 strongly suggest that the red cell vol

Peripheral venous pressure and venous hematocrit

Fig 1 Peripheral venous pressure in mm Hg on the abscissa. Corresponding hematocrit values on the ordinate. N to lack of correlation between the two parameters.

in the first hours of life represents a reliable guide as to the amount of placental transfusion. In the three groups of infants studied, the group with early clamped umbilical cords had also the lowest hematocrit compared to the other two groups (Fig 3) The hematocrits of the early clamped group of infants with a value of 48.35 (S.D 6.09) is significantly lower than the stripped and late clamped groups with a hematocrit of 59.21 (S.D 4.54) and 56.50 (S.D 5.60) respectively This is in keeping with the assumption that the early clamped infants were deprived of a significant amount of placental transfusion.

A variable gradient was found to exist between the central and the peripheral pressure levels (Fig 4) The magnitude of the gradient was not related to the amount of placental transfusion nor to the age of the infant at the time of the pressure reading. (The transition from the central to the peripheral type of pressure is illustrated in Fig 5) The pressure patterns in the central and peripheral positions were significantly different and could not be confused. While a properly placed and well flushed catheter recorded venous pulsations with free excursions in the central position, the peripherally placed catheter registered slight respiratory variations but no venous waves giving the appearance of a mean pressure recording (Fig 6 and 7).

The levels of central venous pressure are related to the height of the hematocrit

Central venous pressure and venous hematocrit levels

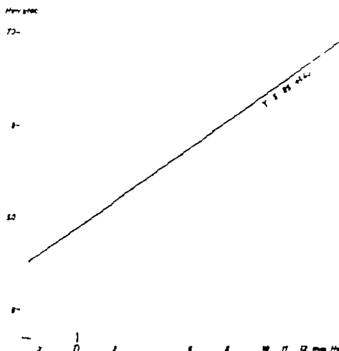
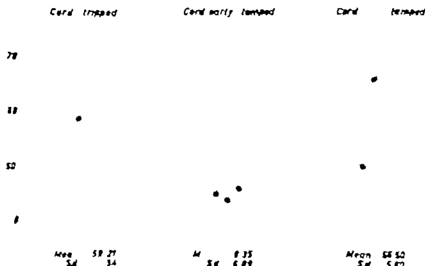


Fig. 2. Central venous pressure in mm Hg on the abscissa and corresponding hematocrit values on the ordinate. Correlation coefficient 0.76.



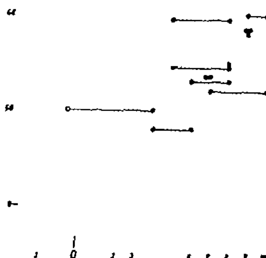


Fig. 4. Pressure gradients recorded in 12 infants and plotted against hematocrit values.

which represents the volume of placental transfusion. On the other hand the pressure recorded in the umbilical recess showed less variability and was not lated to the volume of placental transfusion.

Discussion

The problem of venous pressure in the newborn infant has been studied by a number of investigators. The earliest reports were published by Hasselhorst [1] who recorded pressure in three term infants at

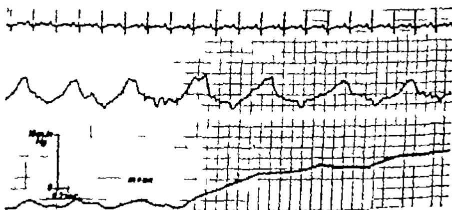


Fig. 5. Electrically integrated mean pull-back pressure tracing from 12 cm to 0 cm catheter tip-cutaneous umbilical distance. From top to bottom: 1. Electrocardiogram lead II. 2. Intra-esophageal pressure. 3. Pull-back pressure curve. Paper speed 25 mm/sec.

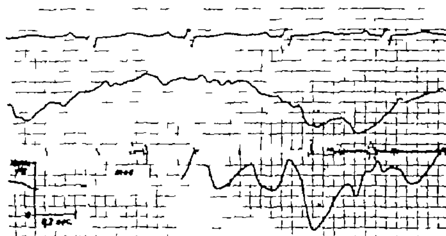


Fig. 6. Central venous pressure recorded 12 cm from the cutaneous umbilicus. From top t bottom: 1. Lead II lectrocardiogram. 2. Intraesophageal pressure. 3. Precordial phonocardiogram. 4. Central venous pressure curve. Paper speed 100 mm/sec

cesarean section with infants still in utero. The mean pressure recorded by him in the vein of the umbilical cord was 26 mm Hg (range 22 mm Hg to 34 mm Hg). These figures were confirmed some 30 years later by Margolis & Orcutt [20]. The pressure recorded by these two authors under identical circumstances were 24 mm Hg mean (range 17 mm Hg to 32 mm Hg).

Wallgren *et al.* [33] recorded pressure in

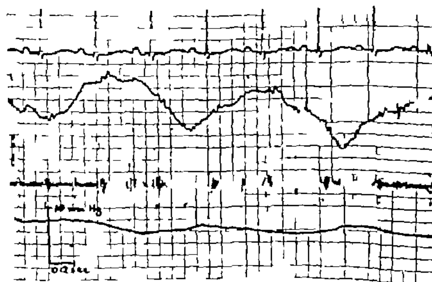


Fig 7. Peripheral venous pressure recorded 6 cm from the cutaneous umbilicus. From top bottom: 1. Electrocardiogram lead II. 2. Intraesophageal pressure curve. 3. Precordial phonocardiogram. 4. Peripheral venous pressure curve. Paper speed 50 mm/sec. Note the absence of venous waves in this recording as compared t their presence in the central pressure curve of Fig. 6

the umbilical vein immediately before and after the first breath of the newborn infant The range of umbilical vein pressure in six infants at 10 sec after delivery was 15 to 50 mm Hg with a rapid fall to 10 to 20 mm Hg at 100 sec. Nyberg & Westin [24] who recorded pressures in a similar fashion reported a mean value of 26 mm Hg in 17 newborn infants.

The pressure values that have been reported by different investigators are very high for a venous system. It is difficult to accept that this magnitude of pressure could be maintained throughout the large veins and the right atrium of the fetus. It appears necessary to assume that a gradient exists between the umbilical vein and the central venous channels A region of resistance to flow must exist between the umbilical vein and the inferior vena cava keeping the pressure high in the umbilical vein but protecting the atrium from the exposure to the high pressure This *resistance to flow is presumably offered* by the ductus venosus with a sphincter mechanism at its distal end and the liver vasculature. Presence of these two collateral routes for the umbilical vein flow has been demonstrated by cinematographic studies in lambs by Barclay [2] and in human living fetus by Lind & Wegelius [17]. Blood flowing into the fetus via the umbilical vein passes to the inferior vena cava by the two routes. directly through the ductus venosus, and indirectly via the portal vein, liver and hepatic veins The presence of a sphincter mechanism is based not only on the variations in the size of the ductus venosus observed by the above-mentioned investigators, but also on the histological findings in the ductus wall of fetal sheep [4]. Indirect pharmacological evidence of the existence of the ductus sphincter is supplied by Dawes *et al* [6] and Gribbe *et al.* [9]. These authors were able to demonstrate dilation of this vessel in response to drugs such as acetylcholine epinephrine, and nor-epinephrine, but not to inert substances like saline

Fig 8 *illustrates diagrammatically the* liver circulation before birth. After closure of the ductus venosus the blood from the portal vein is diverted into the liver area supplied by branches of the umbilical vein. The channel between the portal vein and inferior vena cava has ceased to function. The portal vein system is from now on separated from the inferior vena cava by the liver capillary bed. It may be presumed that the pressure of 7 7 mg Hg mean (range 4 mm Hg to 11 mm Hg) which we have measured in the umbilical recess distal to the ductus venosus after cessation of the placental *flow* represents *the pressure existing in the portal venous system.* Thus the gradient that has been demonstrated in the first hour of life between the umbilical recess and the inferior vena cava represents the difference in pressure existing in the large collecting body veins and the portal circulation The presence of this pressure gradient has been confirmed by others [14] The explanation of this gradient may lie in the fact of a difference in extramural pressure exerted on the venous system in the thoracic and abdominal cavity In the infant studied by us under *fluoroscopic control the transition from* central to peripheral pressure occurred ..5 cm below the dome of the diaphragm, thus well within the abdominal cavity The respiratory pressure fluctuations recorded in the peripheral *position are op-*

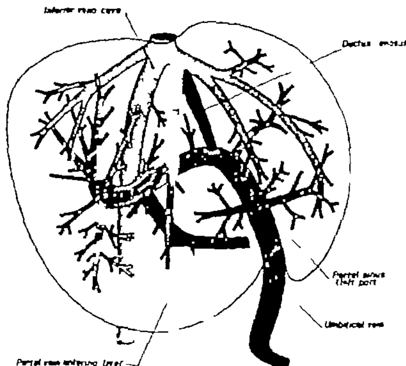


Fig. 8. Schematic representation of anatomical relationship of umbilical vein, portal vessels, hepatic veins, and inferior vena cava. Before cessation of umbilical vein flow the contribution of portal vein to the portal sinus blood is greatly outweighed by the umbilical vein. After clamping of the umbilical cord the vessels indicated by lines are supplied by the portal vein blood only (Barry & Lind).

posed to the respiratory pressure variations in the thorax (Fig 7) and are of much reduced amplitude, indicating transmission of abdominal pressure fluctuations. It is our belief that presence of the narrowed ductus venosus contributes to the existing pressure gradient.

Further confirmation of the assumption that the ductus venosus carries little blood after cessation of the umbilical venous flow may be derived from Fig 9. Indocyanine green dye (1 8 mg) was injected into the right atrium of a 3-hour-old infant and a dilution curve recorded from an ear oximeter. The catheter was then withdrawn to portal sinus position distal to the ductus venosus and another dilution curve was recorded following the injection of the same amount of indocyanine green. The significant distortion of the second curve is obviously not the result of an arteriovenous shunt at the ductus level but due to a slow wash-out of the indicator from the capillary liver bed. The injection into the portal system of indocyanine green and recording of ear oximeter curves resulted in a similar appearance of the dilution curve in eight more infants. The shallow build up slope and absence of the disappearance slope suggest that the bolus of dye has been spread into a trickle during the traverse of the capil

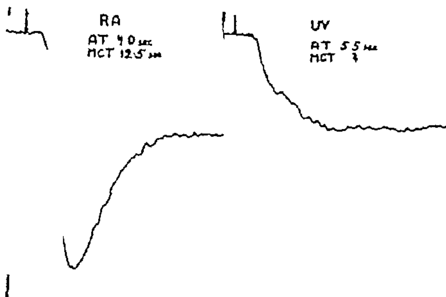


Fig. 9 Left panel: Injection of indocyanine green into right atrium, ear oximeter recording. Right panel, injection of same material into the umbilical vein. Note a prolonged wash-out of dye, longer appearance time and shallow build-up slope

lary bed of the liver. Very little or no dye passed through the ductus venosus and the injected indicator was diverted into the liver capillaries.

The pressure in the portal vein system measured in the first hour of life does not vary with the volume of placental transfusion. The venous pressure however measured in the inferior vena cava or the right atrium reflects the hemodynamic alterations presumably due to the volume of placental transfusion. Our observations are limited to the first hour of life. During this period of time changes in blood volume take place. Mollison *et al.* [22] pointed to the movement of plasma out of the intravascular compartment occurring in the first hours of life. These findings have been confirmed by Gairdner *et al.* [8], Steele [29] and recently by Usher *et al.* [32]. Thus it may be assumed that the blood volume has undergone a significant change during the period of life studied by us. Steele observed a reduction in blood volume during the first two hours of life from 80 ml/kg to 77.5 ml/kg. According to Usher *et al.* as late as four hours after birth the difference in circulating blood volume between children with large and small amounts of placental transfusion was still significant (76 ml/kg in early-clamped infants and 83 ml/kg in late-clamped infants). Thus the movement of plasma was not sufficient to obliterate differences in blood volume caused by the varied amounts of placental transfusion during the period of life studied.

The different behavior of peripheral and central venous pressure in relation to the amount of placental transfusion is in variance to the information supplied by Taylor *et al.* [30]. These investigators measured umbilical venous pressure in the umbilical recess of the newborn infant

with varying amounts of placental transfusion. They concluded from their data that the pressure in the umbilical recess is elevated in the first hour of life in infants receiving a large amount of placental transfusion as compared to infants deprived of it. A number of continuous recordings of pressure changes in the first hour of life illustrate the point From the preceding discussions we are of the opinion that the pressure recorded distally to the ductus venosus does not reflect the pressure existing in the large body veins and in the right atrium

Summary

Central and portal venous pressure in the first hour of life was studied in 24 normal, full term, new born infants with varying amounts of placental transfusion. A gradient between the portal pressure and the central venous pressure was demonstrated in the 11 out of 14 infants The pressure in the central venous system varied with the amount of placental transfusion, whereas the pressure existing distal to the ductus venosus was independent of the blood volume during the first hour of life The central pressure observed in infants that received a large amount of placental transfusion (ten infants) ranged between 0 mm Hg and 10 mm Hg with a mean of 5 7 mm Hg The pressure in the group receiving a lesser amount of placental transfusion (seven infants) ranged between 1.5 mm Hg and 5 mm Hg with a mean of 1 7 mm Hg Pressures obtained distal to the ductus venosus ranged from 4 mm Hg to 11 mm Hg with a mean of 7 7 mm Hg The presence of a narrow ductus venosus channel contributes to the existence of this gradient

Data obtained from dilution curves recorded from right atrial and portal vein injections suggested that little or no blood flows through the ductus venosus during the first hours of lif

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The Blood Volume of the Newborn Infant and Placental Transfusion

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Introduction

The following is the report of an investigation of the blood volume of the normal full-term infant. Previous studies of neonatal blood volume [.., 3 10 11 13] have shown an exceedingly wide range of individual values from 55 to 150 ml/kg

The role of placental transfusion in the size of the blood volume of the newborn is disputed. Numerous studies [1 6 7] have shown that there is an increase in weight of about 100 g during the first 5 minutes of life when the cord is left unclamped. Measurements of blood volume by De Marsh, Windle & Alt [ ] demonstrated the red cell volume to be 40% greater when the cord was clamped late rather than early More recent studies [14], however found no difference in red cell volume when the cord was clamped early or late although higher values were obtained when the cord was stripped

There is disagreement also about the change in blood volume fter birth. Gairdner *et al* [5] have reported that the hematocrit rises immediately after birth. They concluded that this rise in hematocrit is evidence of a decrease in blood volume due to plasma transudation, which might in some infants produce pulmonary edema and hyaline membranes. Sisson & Whalen [1..] on the other hand, have found an increase in both blood volume and hematocrit during the first hours of life suggesting an influx of concentrated blood from a storage reservoir such as the liver More recently Steele [13] has reported postnatal changes in blood volume which differ from those found by Sisson & Whalen. His data show that blood volume decreases after birth due to loss of plasma this decrease being proportional to the height of the hematocrit In none of these reports was consideration given to the possible effect of placental transfusion on the change in blood volume after birth.

The present investigation was designed to measure the blood volume of the normal full term infant at intervals after birth and to determine the amount of the placental transfusion and its relation to changes in blood volume after birth. A dilution technique was employed using I^{131} tagged human albumin.

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Subjects and Methods

The subjects of the present study were 27 full term normal newborn infants born at the Södra Barnbördshuset (Southern Maternity Hospital) Stockholm, to healthy mothers after an uncomplicated labor and vaginal delivery. The infants were delivered between the 38th and 42nd week of gestation, and weighed 2600 to 4600 g at birth. They were admitted to one of three study groups depending on how the umbilical cord was clamped.

1. *Immediate.* Nine infants. One infant had the cord clamped before delivery (loop around the neck), six had their cords clamped within 10 seconds of delivery and two others at 11 and __ seconds.

2. *Delayed.* Eleven infants. The cord was clamped after pulsations ceased about 5 minutes after delivery.

3. *Delayed and stripped.* Seven infants. The cord was stripped firmly toward the infant once every 20 seconds for 5 minutes and was then clamped.

The infants were delivered onto the bed on which the mother was lying and the infants lay about 10 cm below the level of the introitus until the cord was clamped. All were breastfed after a 12-hour fast.

Measurement of blood volume were made four times on each infant at the ages of approximately ½, 4, 24, and 72 hours. Of the 108 determinations, the results of three had to be discarded because of technical difficulties in administration of the dose or in sampling.

Each determination required a 2 ml pre-injection blood sample in a heparinized syringe. Immediately after this sample was taken, approximately 0.75 microcuries of I^{131} tagged human albumin (Atomium) were injected into a scalp vein and flushed through with 2 ml of saline. Five minutes later a 2 ml post injection blood sample was taken. The samples were obtained from the umbilical vein for the ½ and 4 hour measurements, and from the femoral vein at 24 and 72 hours. The veins used for injection (scalp) and for sampling (umbilical and femoral) were remote from each other. In a few infants simultaneous samples were obtained from umbilical and femoral veins 5 minutes after injection of dose and no difference in hematocrit or in radioactivity was found. The maximal dose of I^{131} albumin administered to any one infant was 3.0 microcuries.

A modification of the Volemetron method worked out during this investigation now permits determinations using doses between 0.2 and 0.4 microcuries.

The Volemetron counter [15] was used to measure radioactivity in the dose syringe before and after injection, and in the pre-injection and post-injection blood samples. The final reading was mechanically calculated and expressed as ml blood volume on the basis of a simple dilution formula. The radioactivity of venous blood samples, however is not representative of that in the total blood volume because of the difference between venous and total body hematocrit [10]. Volemetron readings were therefore multiplied by a factor

$$\frac{1 - \text{venous hematocrit}}{1 - 0.87 \text{ venous hematocrit}}$$

to correct for this difference. This correction becomes greater with increasing hematocrit so that with a hematocrit of 40% the corrected blood volume is only 6 % lower than the Volemetron reading while with a hematocrit of 70% it is 22% lower. Plasma and red cell volumes were calculated from the corrected blood volume and the venous hematocrit × 0.87 [10].

The Volemetron counting error was reduced by performing all measurements in triplicate with the aid of paired dose syringes of identical radioactivity. The total error of the method, including sampling, dose administration, and counting was determined by duplicate measurements of blood volume made at ½ hour intervals in 4 infants not included in this study. The error of the method $\sqrt{\frac{\Sigma(d^2)}{2N}}$ was found to be 4.1 %.

Micro-hematocrit measurements were made on each blood sample. The proportion of the red cell column which consisted of trapped

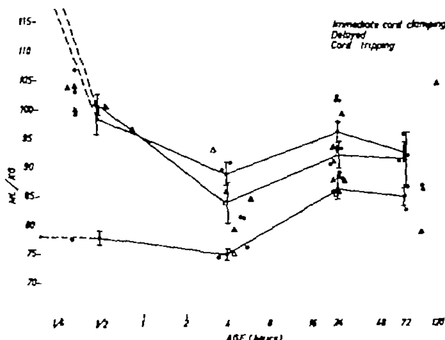


Fig 1 Scattergram of serial measurements of blood volume in nine infants with immediate cord clamping, eleven infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean. Dotted lines represent extrapolations back to the time of cord clamping

plasma was estimated by measuring the radioactivity first of the whole blood and then of the plasma in 10 different samples. These measurements were compared with the microplasma hematocrit measured after 5 minutes centrifugation. An average of 2% of the red cell column was found to be trapped plasma. This result was similar to that found by others [4], and was considered too small to require a correction factor in the present study

Results

The data are presented in Tables I to 3 and in Fig 1 to 4 In the figures, dotted lines are extrapolated back to birth (actually to the time of cord-clamping) These extrapolations are based on the ... that the red cell volume at ½ hour of age was the same as that at time of cord clamping and that the venous hematocrit at birth in members of all three groups was 48 %. (10 cord blood hematocrits on infants other than those in this study averaged 48 %, with a range of 46 to 52 %)

Blood volume (Fig 1)

The blood volume of infants with delayed cord-clamping was estimated to be 1?6 ml/kg at 5 minutes of age and was measured 90 ml/kg at ½ hour 89 ml/kg at 4 hours 96 ml/kg at 24 hours and 93 ml/kg at 72 hours Ten of the 11 infants had ... decreases in blood volume between

TABLE I *Cord-clamping*

Case no	Age	Birth weight g	Present weight g	Body length cm	Gestation wks	Venous Hct %	Volumetron reading ml	Blood vol. ml	Blood vol. ml/kg	Plasma vol. ml	Plasma vol. ml/kg	RBC vol. ml	RBC vol. ml/kg
						Immediate cord-clamping							
1	22 m	2560	2560	47	39½	46.0	213	194	75.7	117	45.5	77	30.[illegible]
	5½ h		2560			49.5	200	178	69.5	101	39.5	77	30.0
	5 d 0 h		2390			44.0	202	184	[illegible]	114	[illegible]	70	29.[illegible]
2	4 m	2680	2680	47	40½	43.0	231	229	79.4	144	49.7	85	[illegible]
	4½ h		2680			44.0	230	[illegible]	72.8	121	45.4	81	26.2
	46 h		[illegible]			43.0	[illegible]	228	83.7	143	[illegible]	85	31.2
3	30 m	3020	3020	48	[illegible]	60.5	300	[illegible]	83.5	119	39.5	123	44.0
	5½ h		3020			62.0	[illegible]	230	76.2	106	35.1	124	41.[illegible]
	23 h		[illegible]920			64.0	260	244	83.4	129	44.2	115	39.2
	96 h		2860			51.5	[illegible]	248	86.[illegible]	137	47.8	111	38.8
4	14 m	3150	3150	49	41	44.0	257	234	74.3	144	45.9	90	[illegible]
	4½ h		3150			44.0	[illegible]	239	75.8	148	46.8	91	29.0
	19 h		3050			39.8	237	264	86.3	173	56.7	91	29.8
	46 h		3000			41.0	260	236	78.9	152	50.6	84	28.3
5	20 m	3420	3470	49.5	40	46.5	[illegible]	[illegible]46	71.8	147	42.8	[illegible]	29.0
	5½ h		3420			43.0	262	258	75.2	157	45.9	101	29.4
	4 h		[illegible]			39.0	330	304	93.4	[illegible]00	61.6	104	31.8
	95 h		3325			42.0	305	[illegible]	88.0	174	53.6	104	[illegible]
6	20 m	3480	3480	49	39	42.0	308	260	80.5	[illegible]	50.5	104	30.0
	2½ h		3480			45.0	[illegible]85	259	[illegible]	158	45.3	101	[illegible]
	25 h		3370			48.0	262	[illegible]66	[illegible]	160	49.0	[illegible]	[illegible]
	67 h		3230			44.0	284	[illegible]	82.1	165	51.[illegible]	103	31.9
7	60 m	3500	3500	51	40	[illegible]	308	284	81.0	180	51.5	104	29.[illegible]
	5½ h		3300			30.5	305	281	80.3	184	52.7	97	27.8
	25 h		3430			40.5	250	[illegible]94	83.8	190	53.7	104	30.1
	76 h		3[illegible]0			33.5	280	[illegible]60	[illegible]	173	50.6	87	[illegible]
8	50 m	3620	3620	50	41½	51.0	320	282	[illegible]	[illegible]	42.4	125	34.4
	3½ h		3620			53.0	330	264	78.4	148	40.9	136	37.5
	[illegible]6 h		3460			47.0	338	304	87.9	180	51.9	124	35.8
	68 h		3360			47.5	330	[illegible]97	88.4	174	51.8	123	36.6
9	70 m	4010	4010	52	40	50.0	352	314	78.4	177	44.2	137	34.1
	4½ h		4010			47.5	331	298	[illegible]	174	43.4	124	30.7
	24 h		3890			[illegible]	378	346	88.9	220	56.5	126	32.4
	5 d 0 h		3650			[illegible]	348	314	81.6	198	51.5	118	30.1
						Delayed cord-clamping							
10	22 m	2830	2830	48	42	84.0	347	302	106.7	160	56.5	14[illegible]	[illegible]
	3½ h		2830			70.5	298	229	81.2	[illegible]	31.3	140	49.8
	55 h		2710			60.5	[illegible]	239	88.3	114	41.8	1[illegible]5	46.5
	73 h		[illegible]680			60.5	277	222	82.7	[illegible]	34.8	129	47.9
11	6 h	3520	3520	50.5	41	60.5	413	318	90.4	126	36.0	192	54.5
	17 h		3390			63.0	427	337	99.5	125	40.0	199	58.9
	48 h		3310			67.0	387	306	92.5	128	38.6	178	53.7
12	24 m	3700	3[illegible]00	50	40	54.0	443	381	102.9	195	52.7	183	50.2
	4½ h		3700			60.5	413	317	93.5	164	44.4	183	49.4
	26 h		3650			57.5	403	34[illegible]	97.0	171	48.4	171	49.6
	72 h		3600			57.0	410	348	96.8	176	45.7	172	49.1

Table 1 (cont.)

Case no.	Age	Birth weight g	Present weight g	Body length cm	Gestation wks	Venous Hct	Volemetron reading ml	Blood vol. ml	Blood vol. ml/kg	Plasma vol. ml	Plasma vol. ml/kg	RBC vol. ml	RBC vol. ml/kg
13	30 m	3750	3750	50	41	58.0	406	344	91.8	170	45.4	174	46.4
	7 h		3750			58.5	390	332	88.4	163	43.4	169	45.0
	24 h		3560			62.0	402	329	92.5	149	41.8	180	50.7
	74 h		3400			55.5	353	290	85.5	147	4[illegible].4	152	44.1
14	45 m	3750	3750	51	37	56.0	478	411	109.5	211	56.3	200	53.3
	4½ h		3750			60.0	405	340	90.6	162	43.3	178	47.5
	25 h		3700			60.0	446	375	101.3	179	48.5	196	52.9
	5 d 1 h		3510			56.0	421	36[illegible]	103.1	186	[illegible]	1[illegible]6	50.2
15	35 m	3890	3880	53	41½	68.0	415	328	84.5	134	34.4	194	50.1
	6 h		3880			67.0	410	324	83.5	135	34.9	189	48.6
	24 h		3660			61.0	440	373	102.0	176	4[illegible].9	197	54.1
	66 h		3590			61.0	395	328	91.3	154	43.0	1[illegible]4	48.3
16	20 m	3880	3880	53	40½	65.5	478	380	98.0	163	42.1	217	55.9
	5 h		3880			[illegible]1.0	422	321	82.7	123	31.7	198	51.0
	21½ h		3750			67.5	429	339	90.4	140	37.3	199	53.1
	4 d 21 m		3720			64.5	442	358	96.3	157	42.2	201	54.1
17	28 m	3950	3950	52	40	63.0	4[illegible]8	351	88.8	159	40.3	192	48.6
	5½ h		3950			64.5	456	369	93.5	162	41.0	207	5[illegible].5
	24 h		3900			60.0	472	396	101.7	169	43.7	207	53.0
	71 h		3790			60.0	413	347	91.5	166	43.7	181	47.8
18	21 m	4200	4200	51	41	50.0	490	416	99.1	206	49.1	210	50.0
	8½ h		4200			63.5	427	341	81.3	147	34.9	194	46.4
	29 h		4090			63.0	439	352	86.0	159	38.8	193	47.2
19	45 m	4210	4210	51.5	42	57.5	532	452	107.3	225	53.6	227	53.7
	5½ h		4210			60.5	516	434	103.0	205	48.8	229	54.3
	24 h		4050			50.0	475	399	98.5	194	48.0	205	50.5
	5 d 5 h		4030			56.0	421	352	88.5	186	46.1	1[illegible]6	43.7
20	27 m	4600	4600	54	41	56.0	518	446	97.0	228	49.7	218	47.5
	3½ h		4600			58.0	488	412	89.7	204	44.3	208	45.4
	24 h		4520			57.0	518	441	97.5	222	49.1	219	48.4
	70 h		4340			56.0	482	414	95.5	212	49.0	202	46.5

½ hour and 4 hours, and an increase between 4 and 24 hours.

The blood volume of infants with stripped cords was not significantly different from those with delayed clamping. There was the same tendency for the blood volume to fall between ½ and 4 hours of age (all seven infants) and to rise again between 4 and 24 hours (five out of seven infants).

Infants with immediate cord-clamping had an estimated blood volume of 78 ml/kg at birth and a measured volume of 8[illegible] ml/kg at ½ hour, 75 ml/kg at 4 hours, 86 ml/kg at 24 hours, and 8[illegible] ml/kg at [illegible] hours. These values are significantly lower than those with delayed cord-clamping for all but the 4 hour determination. There was no tendency for blood volume to decrease between ½ and 4 hours of age with immediate clamping although all nine infants had an increase in blood volume between 4 and [illegible] hours.

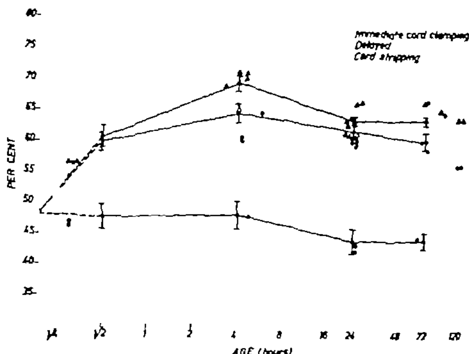


Fig. — Scattergram of serial measurements of hematocrit in nine infant with immediat cord clamping, leven infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean. Dotted lines represent xtrapolations back t the time of cord clamping.

Venous hematocrit (Fig ?)

The venous hematocrit rose in infants with delayed cord clamping from an estimated 48 % at birth to 60 % by ½ hour and 64 % by 4 hours. It then fell to 61.5 % and 60 % at 24 and 72 hours. Hematocrit values were similar in infants whose cords were stripped.

Infants with immediate cord-clamping showed no rise in hematocrit after birth the estimated cord blood hematocrit and the ½ hour and 4 hour measurements were all about 48 %. The hematocrit then fell to 44 % at 24 and ~ hours

Red cell volume (Fig 3)

Delayed cord-clamping resulted in a red cell volume of 51 ml/kg at ½ hour of age This was 61 % larger than the 32 ml/kg red cell volume found after immediate cord clamping ($P - 0.001$) Infants whose cords were stripped had red cell volumes similar to those with delayed clamping

There was not an appreciable change in red cell volume per kg body weight during the first ~ hours of life in any of the 27 infants. In no instance did serial determinations on the same infant vary by more than 15 %.

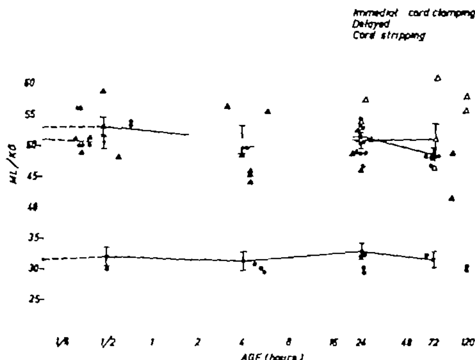


Fig. 3. Scattergram of serial measurements of red blood cell volume in nine infants with immediat cord clamping, eleven infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean. Dotted lines represent extrapolations back to the time of cord clamping

Plasma volume (Fig 4)

Infants with delayed cord-clamping had an estimated plasma volume at the time of cord-clamping of 70 ml/kg The plasma volume then decreased to 48 ml/kg at ½ hour and to 39 5 ml/kg at 4 hours Following this, it increased to 44 ml/kg t 4 and 72 hours Plasma volumes obtained after cord-stripping were essentially similar

With immediate cord-clamping the plasma volume t birth was estimated at 46 ml/kg and it was 46 and 44 ml/kg at ½ hour and 4 hours of age The plasma volume then increased and wa 54 and 51 ml/kg at "4 and 7" hours.

Analysis of f ndings

These data indicate that there was a 61 increase in blood volume during the first 5 minutes of life when cord-clamping was delayed. This placental transfusion amounts to 106 ml for a 3500 g infant. Cord-stripping did not significantly augment this transfer of blood

The blood volume did not change during the first hours of life following immediate cord-clamping but in infants with delayed cord-clamping there was a decrease of 30 5 ml/kg during th first 4 hours due to a loss of plasma. For a 3500 g infant this plasma loss would amount to 107 ml, 7" ml

TABLE 2 *Cord-stripping*

Case no.	Age	Birth weight g	Present weight g	Body length cm	Gestation wks	Venous Hct %	Volemetron reading ml	Blood vol. ml	Blood vol. ml/kg	Plasma vol. ml	Plasma vol. ml/kg	RBC vol. ml	RBC vol. ml/kg
1	10 m	2920	2970	48.5	40	56.8	232	304	104.0	155	52.9	149	51.1
	4½ h		2920			64.5	310	231	80.0	110	37.7	141	49.3
	24 h		2800			61.5	290	41	86.0	11	40.0	179	46.0
	96 h		2700			62.0	297	42	89.8	11	41.3	130	49.5
22	38 m	3020	3020	50	41½	55.0	31_	304	100.7	158	52.3	146	49
	4½ h		3020			_1.0	283	215	71._	83	[illegible]	132	44.1
	27 h		2900			60.5	328	254	87.6	107	36.9	147	50.
	72 h		_880			66.5	_88	230	80.1	97	33.6	133	46.2
23	31 m	3280	3340	50	4	56.5	3_8	325	98.7	165	50.7	160	49.0
	4½ h		3260			70.0	319	246	76.3	96	29.8	150	43.8
	22½ h		3180			61.5	345	286	90.9	133	42._	153	48.7
	94 h		3210			60.0	30_	254	79.0	131	37.8	133	41._
24	30 m	3310	3310	49.5	4	63.0	433	355	107.2	180	49.5	185	55.9
	3½ h		3310			69.0	395	306	93.2	123	37.1	185	55.9
	36 h		3280			68.0	407	328	99.3	139	42.3	187	57.0
	4 h		3120			65.0	418	334	107.9	143	46.3	189	60.5
25	35 h	3490	3490	49	40	67.5	477	337	96.8	140	39.8	197	57.0
	6½ h		3480			75.0	420	285	84.8	103	29.5	182	55.3
	4 h		3400			61.0	412	342	100.5	160	4_	182	53.3
	5 d 0 h		3300			63.5	40	330	100.0	147	44.7	183	55.3
26	21 m	3640	3650	50	40½	62.0	457	380	104.0	175	48.0	_05	56.3
	4 h		3650			71.0	467	356	97._	136	37.1	219	60.2
	22 h		3540			62.6	412	334	92.6	149	41.9	185	51.3
	5 d 1 h		3650			63.5	470	381	104.3	170	46.7	11_	57.6
27	4 m	3650	3650	51	39	63.0	418	343	92.8	155	4_.6	189	51.2
	4½ h		3650			65.6	263	291	79.8	1_	34._	186	45.5
	22 h		3590			62.0	283	316	8_.8	143	38.8	173	45.9
	94 h		3420			65.0	243	278	81.0	121	35.2	157	45.8

during the first ½ hour and the remaining 30 ml by 4 hours of age. Between 4 and 24 hours of age there was an increase in plasma volume in all but two infants averaging 22 ml per infant, which was not related to the method of cord-clamping.

There was little or no change in any of the parameters between measurements obtained at 24 and 72 hours of age. The hour determinations showed that infants with delayed cord-clamping had a significantly larger blood volume (93 ml/kg) than infants with immediate cord clamping (82 ml/kg) (P 0.001). Their hematocrits were also higher 60 as compared with 44% (P 0.001).

Correlations between hematocrit, blood volume, red cell volume and plasma volume in individual infants at 72 hours of age are found in Fig. 5–8. There was a correlation (Fig. 5) between hematocrit and red cell volume (P 0.001) which could be approximately expressed as follows: *red cell volume in ml/kg = hematocrit in per cent – 12*. There was also a correlation (Fig. 6) between hematocrit and blood volume (P 0.01). An inverse correlation (Fig. 7, 8) obtained between hematocrit

PLASMA VOLUME

Immediate cord clamping
Delayed
Cord stripping

ML/KG

AGE (hours)

Fig. 4. Scattergrams of serial measurements of plasma volume in nine infants with immediate cord clamping, eleven infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean. Dotted lines represent extrapolations back to the time of cord clamping.

and plasma volume ($P < 0.001$) and between red cell volume and plasma volume ($P < 0.03$). It can therefore be stated that with increasing volumes of placental transfusion and thereby of red cells, there was at 72 hours of age a proportionately higher hematocrit, a smaller plasma volume and a larger blood volume.

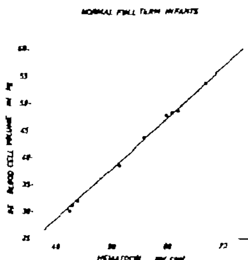


Fig. 5. Correlation between hematocrit ( ) and red blood cell volume (y) in 16 infants about 72 hours of age. The regression line can be derived from the formula y 10.06 0.9600x and the slope of this line is statistically significant (P 0.001). The standard deviation about the line is 4.4.

TABLE 3

	½ hr	4 hrs	24 hrs	72 hrs
	Mean values ± standard error of the mean			
Hematocrit (%)				
Early	47.3 ± 2.0	47.9 ± 2.3	43.6 ± 2.0	43.8 ± 1.3
Late	59.2 ± 1.5	64.1 ± 1.5	61.5 ± 1.1	60.3 ± 1.4
Stripped	60.5 ± 1.7	69.4 ± 1.4	63.3 ± 0.8	63.6 ± 0.8
Blood volume (ml/kg)				
Early	78.0 ± 1.3	78.3 ± 1.0	86.3 ± 1.8	82.3 ± 1.4
Late	98.6 ± [illegible]6	88.9 ± 2.0	98.9 ± 1.7	92.6 ± 1.8
Stripped	100.9 ± 1.7	83.9 ± 3.5	92.3 ± [illegible]	91.6 ± 4.6
Plasma volume (ml/kg)				
Early	45.9 ± 1.3	42.9 ± 1.7	53.5 ± 2.2	50.8 ± 0.7
Late	48.0 ± 2.3	39.5 ± 1.8	44.6 ± 1.4	44.1 ± 1.7
Stripped	47.8 ± 1.9	33.3 ± 1.7	41.5 ± 1.[illegible]	40.8 ± 2.0
Red blood cell volume (ml/kg)				
Early	3[illegible]1 ± 1.6	31.4 ± 1.6	32.7 ± 1.4	31.6 ± 1.3
Late	50.6 ± 0.9	49.5 ± 1.0	51.3 ± 1.1	48.4 ± 1.1
Stripped	53.1 ± 1.6	50.7 ± 2.4	50.8 ± 1.4	50.7 ± [illegible]7
	Significance of differences (t-test)			
Hematocrit				
Early-late	+ + +	+ + +	+ + +	+ + +
Late-stripped	−	+	−	−
Early-stripped	+ + +	+ + +	+ + +	+ + +
Blood volume				
Early-late	+ + +	+ + +	+ +	+ + +
Late-stripped	−	−	−	
Early-stripped	+ + +	+	−	+
Plasma volume				
Early-late	−	−	+ +	+ +
Late-stripped	−		−	
Early-stripped	−	+ + +	+ + +	+ +
Red blood cell volume				
Early-late	+	+ +	+ +	
Late-stripped	−	−		−
Early-stripped	+ + −		+ + +	

− $P > .05$
+ P 0.05 − 0.01
+ + P 0.01 0.001
$P < 0.001$

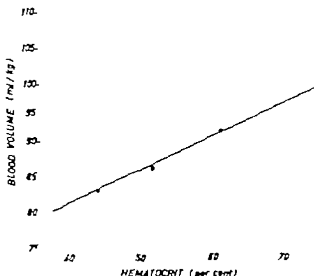


Fig. 6. Correlation between hematocrit (x) and blood volume (y) in 26 infants about 72 hours of age. The regression line can be derived from the formula $y = 63.00 \; 0.4643\, x$ and the slope of this line is statistically significant ($P = 0.01 - 0.001$). The standard deviation about the line is 7.63.

Discussion

The results of this study demonstrate a larger placental transfusion than has previously been reported. What is the significance of 61% increase in blood volume during the first five minutes of life? Is this a physiological process and if physiological, what are the effects of its deprivation? Does this transfusion consist of blood which belonged to the fetus *in utero* and left the infant transiently during delivery or does it represent a massive over-expansion of the infant's circulation at birth? Does the blood transfusion help to expand the lungs by capillary erection [8], or does expansion of the lungs cause the placental transfusion by increasing the pulmonary vascular bed?

Although this study did not purport to answer these questions it is possible to examine the results in relation to them. Infants with delayed cord-clamping showed the normal neonatal plethora while infants whose cords had been clamped immediately were blanched for 6 to 1 hours. Neither group, however, showed any tendency to develop respiratory distress, nor was the onset of respirations slower in one than in the other.

Analysis of red cell volumes obtained when the umbilical cord was clamped at different intervals after birth suggests that the rate of the placental transfusion is exceedingly rapid during the first seconds of life and then becomes progressively slower (Fig. 9). One-quarter of the placental transfusion or about 40 ml of blood enters the infant within 15 seconds, and one half (90 ml) within 60 seconds after birth.

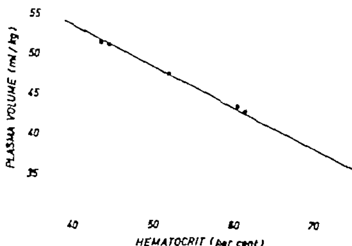


Fig. 7 Correlation between hematocrit (x) and plasma olume (y) in 26 infant bout hours of age The regression line can be derived from the formula $y = 73.15 - 0.4975x$ and the slope of this line is statistically significant ($P < 0.001$). The standard deviation bout the line is 2.72.

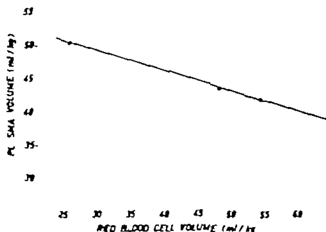


Fig. 8. Correlation between red blood cell lume (x) and plasma olume (y) in 26 infan t at hours f age The regression line can be derived from the formula y 58 15 0.2017 and the slope of th line is statistically significant (P 0.05 0.01). The standard deviation about the line is 3.29

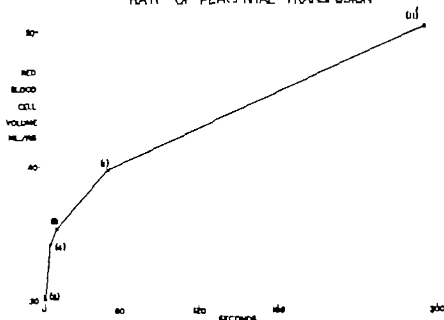


FIG. 9. Rate of placental transfusion as indicated by erage red blood cell olume t ½ hour of age following cord clamping at different intervals after birth. These include the 20 infant who comprised the immediate and delayed cord lamping groups, with the addition of seven more infants whose cords were clamped at varying times during the first minut f life. The figures in parentheses indicat the number of infants studied during each time interval.

Further studies were performed to determine whether the placental transfusion could be due to the increase in pulmonary blood volume coincident with expansion of the lungs. Five pairs of infants were compared, in each of the pairs the time of cord clamping being the same (4 6, 8 11 or 15 seconds). One infant of each pair was breathing *before the cord* as clamped while the other had not as yet breathed. The blood volume and hematocrit were measured about ½ hour of age No difference was found between the red cell volume of the infants who had breathed and of those who had not breathed at the time f cord-clamping (Table 4) It wa therefore concluded that the immediate post natal transfer of blood from placent to fetus was not related to expansion of the lungs.

There was a marked decrease in blood volume from 1.5 to 90 ml/kg during the first 4 hours of life following a placental transfusion.

The blood volume at 7* hours of age tended to stabilize around one of two dif *ferent volumes depending on the time of* cord-clamping. Infants with immediate cord-clamping had an average blood vol ume of 8* ml/kg with a 44 hematocrit. Those with delayed cord-clamping had an average blood volume of 93 ml/kg with a 61 hematocrit

This investigation demonstrates that the wide individual variation which was found in the previous studies of blood vol

TABLE 4

Cord clamped before breathing		Cord clamped after breathing		
Age at clamping sec	Red blood cell volume age ½ hr ml/kg	Age at clamping sec	Red blood cell volume age ½ h ml/kg	Difference Red blood cell volume ml/kg
4	30.4	4	29.5	0.9
6	29.6	6	28.0	1.6
8	29.0	8	31.3	−2.3
11	37.8	11	34.3	3.5
15	36.7	15	39.6	−2.9

ume in newborn infants can in large part be attributed to variations in time of cord clamping and therefore to the amount of placental transfusion. Infants who received no placental transfusion had values during the first hours of life which were very close to the mean values of a 78 ml/kg blood volume a 48 % venous hematocrit and a 32 ml/kg red cell volume Infants who received a placental transfusion had a greater blood volume, hematocrit and red cell volume the amount of the increase depending on the volume of the transfusion.

Some of the individual variation found previously may also have been due to the use of less accurate methods of measurement In none of the previous studies of neonatal blood volume were estimations of duplicate error of the method reported. The 4 % error in the method used here prevented the otherwise unaccountable changes in red cell volumes over a two-day interval in the same infant which have previously been reported to be as great as 15 to 40 % [14]. Serial measurements of red cell volume four times in three days in the present study varied by less than 10 from those which preceded or followed in 14 of the 105 determinations, and variations in no infant exceeded 15 %

There was found a 22 ml increase in plasma volume between 4 and 24 hours of age This expansion of the circulation could be due to a generalized decrease in vascular tone but there is no reason to suspect that such a decrease in tone does occur at this age. It would seem more likely there is an increase in circulation to some part or parts of the body Such a local increase in circulation could occur in the gastrointestinal tract where there is a change between 4 and 24 *hours of age from a state of* inactivity to one of active function. Angiographic studies of the neonatal circulation have shown a marked increase in the gastrointestinal circulation at this period of life

Conclusions

The normal full-term infant delivered by vagina receives a placental transfusion amounting to 61 % of its original blood volume if the cord is not clamped for 5 minutes after birth Most of this transfused blood leaves the circulation in the *form of a transudation of one half of the* plasma volume during the first 4 hours of life The cardiovascular and pulmonary effects of this extreme vascular distention

and subsequent plasma transudation are not known. Concomitant with the increased red cell mass resulting from a placental transfusion, there must also be an increase in neonatal bilirubin formation and in the iron store during infancy

The 22 ml increase in plasma volume between 4 and 24 hours of age is believed to be due to a localized increase in the circulation to some part of the body such as the gastrointestinal tract. The final blood volume of the newborn infant once stabilized after 24 hours of age, varies directly with the hematocrit which is in turn a function of the volume of placental transfusion.

Summary

Serial blood volume measurements were made in 27 normal full term newborn infants using iodinated human albumin. At the moment of birth the newborn infant was estimated to have a blood volume of 78 ml/kg with a venous hematocrit of 48 %. When the cord-clamping was delayed for 5 minutes the blood volume increased by 61 % to 126 ml/kg This placental transfusion amounted to 166 ml for a 3,500 g infant, one-quarter of which occurred in the first 15 seconds, and one-half within 60 seconds of birth. Stripping of the umbilical cord 10 times during the 5 minutes did not increase the volume of the transfusion.

When the placental transfusion was prevented by immediate clamping of the cord, the blood volume did not change appreciably during the first 4 hours of life On the other hand, there was a marked decrease in blood volume from 126 to 80 ml/kg during the first 4 hours in infants who had received a placental transfusion. This decrease was brought about by the transudation of one-half of the original plasma volume so that the venous hematocrit rose from 48 % at birth to 64 % by 4 hours

In all but three of the infants studied there was an increase in blood volume between 4 and 24 hours of age which was due to an increase in plasma volume averaging 22 ml per infant. There was no appreciable change in blood volume between 24 and 72 hours of age

The red cell volume remained stable during the first three days of life in each of the infants those who had received a placental transfusion maintained a red cell volume about 60 % larger than those who had not.

At 72 hours of age the blood volume had stabilized after the plasma shifts of the first day of life and the range of values extended from 75 to 107 ml/kg This variation between individuals was due in large part to differences in hematocrit which ranged from 39 % to 67 %, and these in turn were related to the volume of placental transfusion.

Average values at 72 hours for infants who had received no placental transfusion were 82 ml/kg blood volume 31 ml/kg red blood cell volume 51 ml/kg plasma volume and 44 % venous hematocrit. For infants who had received a placental transfusion they were 93 ml/kg blood volume, 49 ml/kg red blood cell volume, 44 ml/kg plasma volume and 60 % venous hematocrit.

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The Body Density of Newborn Infants

by BENT FRIIS-HANSEN

The interest in the composition of the human body has been increasing in recent years because metabolic studies have shown that "body weight" is too loose a unit of reference to use when finer changes in the external balance of the body have to be defined. For example changes in body weight may be the result of such widely different changes of the body components as changes in total body water, changes in the cellular mass or changes in the amount of fat tissue. Pioneer work in the study of body composition has been carried out by Behnke [2] and by Moore [4] and their collaborators.

In adults the measurements of body density have proved to be an important parameter as an indirect way of measuring the fat content of the body. The classical method for this determination is the Archimedes principle by which the volume of a body is measured by weighing before and during total submersion under water (the hydrostatic method) or by measuring the amount of water displaced by the body (the water displacement method). In the human subject a correction for the air volume in the respiratory tract (and the gastrointestinal tract) has to be introduced and both these methods require a certain cooperation from the subject for which reason they are not suitable for use in infancy and as a consequence very few determinations of the density of the living newborn infants have ever been carried out.

In a previous paper a preliminary report [6] was given of a method which has been developed to overcome some of these difficulties, and a few preliminary results were given. The principle of this method is that the volume of air in a closed system can be calculated from the pressure changes after a known amount of air has been introduced into the system.

A somewhat similar principle was used in 191 by Pfaundler [13] who measured the body volumes of dead infants by measuring pressure changes after having induced changes in the volume of a closed cylinder by a piston-like action of the end wall, and Murlin & Hoobler [11] measured the density of children by pressure changes in a respiration incubator using the same technique as Pfaundler. Later Kohlrausch [9] in 1930 measured the volume of living dogs and dead infants in a steel box into which air was pumped from a burette and the pressure changes

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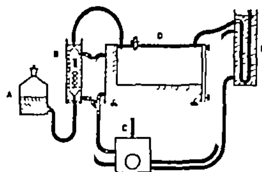


Fig. 1 An instrument for measuring the body density of infant as described in the text.

were recorded. Recently the volume of the living subject ha been measured in a closed system where the air volume is determined by Helium dilution [5 15]. An extensive review of the work done up to 1933 was given by Boyd [3].

The following is an extensive description of the method with a discussion of its accuracy and some results obtained in full-term normal babies.

Method

The air volume within n air tight chamber can be measured by observing the increase in pressure which takes place when a known amount of air is pumped into the hamber. When a baby is placed in the hamber and the experiment i repeated there i less ir in the chamber and the pressure re increases accordingly higher. The volume of the baby may then be calculated as

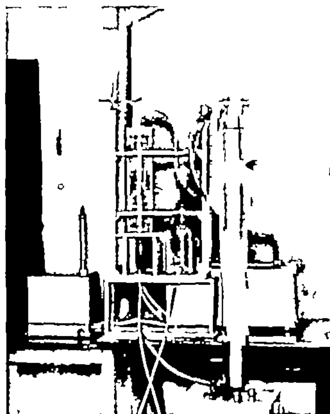


Fig — A photograph of the instrument. The pressure chamber itself is seen in he background t the right

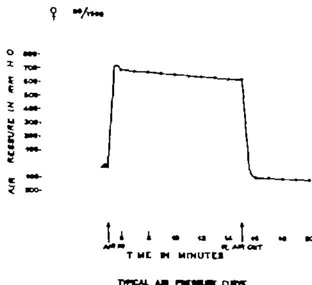


Fig. 2. Air pressure curve obtained with an infant in the chamber

the difference between the two measurements.

The instrument which has been constructed for this purpose is shown in Figs. 1 and 2. It consists of air-tight chamber (*D*) with volume of bout 15,000 ml. It has a Plexiglass window at the top. The baby can be placed in the chamber by removing the lid which is placed at one end of the chamber. This lid is well isolated by cork plates and can be closed air-tight by six screws. This hamber is connected to a water-manometer (*E*) and 1000 ml burett (*B*) by thick rubber tubing (vacuum tubing). The manometer is filled with coloured solution with den sity of 1 000 t room temperature. Finally there is stopcock in the top of the hamber connecting this to the room air. Both the chamber the burett and the manometer are surrounded by water jacket in which the water i kept circulating t constant temperature by the cycloterm (*C*) (an lectric pump with thermostatic regulated heater). Finally the burett is connected t a water flask (*A*). The temperature of the room is kept constant at 25°C and the apparatus t 35 C.

One to two hours before measurement is made a wet diaper is placed in the chamber in order to obtain saturated water vapour inside the instrument. When equilibrium has been obtained the stopcock is closed and the pressure measured on the manometer should remain exactly t 0 for the following 5 minutes. Otherwise equilibrium will not yet have been obtained. The water flask is then raised whereby the air in the burett is pumped over int the chamber and then the water circulation surrounding the burette is disconnected because the water now flowing into the burett is at room temperature which will disturb the temperature equilibrium of the pparatus.

The pressure is then read on the manometer at every minut. The initial high pressure decreases by 5–10 mm during the first 2–3 minutes (due to the relative slow compressability of the air and the accumulated heat has to be given off), but after 3 minutes the pressure shall remain constant. If it continues t fall this indicates leak. When the pressure has been constant at the third, fourth and fifth minut the water in the burett is allowed t flow back into the water

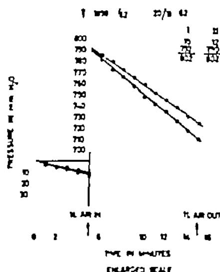


Fig 4 Ai pressure curves from two measurements on the same infant the air pressure being drawn on an enlarged scale

flask nd the water circulation to the jacket surrounding the burett is re-opened The stopcock I opened again and after 5 minutes the experiment i repeated

The volume of the chamber is calculated from the formula

$$\frac{P(V+1000)}{T} = \frac{(P+p)V'}{T'}$$

where V is the volume of ai in the empty chamber plu the connection tubes P is the barometric pressure minus the pressure o saturated water vapour t the given room temperature calculated in mm H_2O The *barometric pressure is measured on mercury barometer which can be read to 0 1 mm* Hg p i the increase in pressure in mm H_2O and T and T' are the absolute temperature during the experiment At constant temperature this can be written as

$$V = P/p$$

When constant result have been obtained in two consecutive measurements, this value V taken as the volume of the empty box on that given day This can vary from d y to day according to the size of the diaper and the amount of water used for wetting it Actually only minor variations ar found.

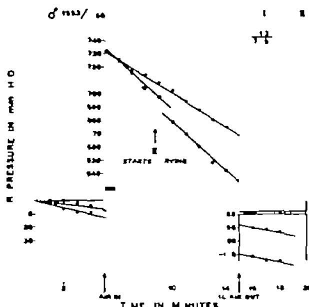


Fig. 5 Curves simila t those in Fig. 4 but break is seen in curve II when the infant started crying

Table 1 The body density and gestational age sex length, weight and body vol me of 29 newborn infants all measured within the first 24 hrs of l fe

Gestational age, weeks	Se	Length, cm	Weight, g	Volume ml	Denst g/ml
38	♂	53	3350	3324	1.004
39	♀	50	3060	2927	1.046
39	♂	51	3050	3035	0.990
39	♂	51	3220	3028	1.064
39	♂	53	3360	3398	0 989
39	♂	54	3960	3946	1.004
40	♂	50	2630	2544	1 037
40	♂	50	2910	*738	1.064
40	♀	50	2910	833	1 038
40	♀	52	2980	2821	1 060
40	♂	51	3140	3348	1.031
40	♂	5_	3140	3014	1 04
40	♀	52	3160	31 3	0.99
40	♂	51	3420	3372	1.017
40	♀	5_	3330	3637	0 971
40	♂	32	3870	3673	1.034
40	♂	52	3940	3901	1.01(
?	♀	31	3000	*768	1.093
?	♀	50	3100	2013	1.063
?	♂	52	3390	3480	1.032
41	♂	53	3190	*850	1 090
41	♀	52	3190	3257	0.990
41	♀	54	34 0	3344	1 038
41	♀	53	3630	3379	1.036
41	♀	53	3670	3548	1.029
41	♀	54	3750	3704	1.012
42	♀	51	3350	3364	0.996
43		51	3460	3241	1 059
43	♀	51	3620	3563	1.015

A newborn, nude baby is then placed n the chamber which has a volume of about 15 liters, but first plastic catheter put down int the stomach through the nose the stomach has been emptied and the catheter is l ft open t connect the air in the stomach directly t the air surrounding the baby so that no pr ssure gradient will exist When the baby is breathing evenly and not crying the airways t the lungs are also open and both the air in the respiratory tract and in the stomach will participat in the pressure increase during the measurement and no correction for those ir volumes ha t be introduced in the final calculation of the volume of the baby Unfortunat ly the ir in the bowels cannot be excluded in this way but when the abdominal wall is relaxed the air in the bowels will lso participat in the pressure changes t some extent.

The baby is then left in the chamber for 15 minutes until the skin temperature ha reached equilibrium with the temperature of the chamber During this period the lid is left only partly closed, that is with a gap of 1 cm t one end, and direct measurement ha e shown that under these conditions the concentration of oxygen in the box will not fall significantly After 15 minutes the lid and the stopcock are losed, and the pressure is read t every minut for 5 minutes. Now the pressure will often decrease gra dually due t the fact that the respiratory quotient of the baby is usually below 1 0. If the pressure increases it is a sign that temperature equilibrium has not yet been ob-

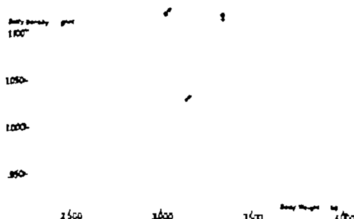


Fig 6 The body density plotted against body weight.

tained nd further time ha to be allowed for equil brium. After 5 minutes 1000 ml of air is again pumped into the hamber and the pressure is read for another 10 minutes. Pressure curve are then obt ined, as shown in Fig 3 nd on an enlarged scale in Fig 4 When the baby remain quiet during the experiment straight line curves are obtained and fter 15 minutes the experiment is stopped. The pressure is released by letting the w ter out of the burett and the chamber opened and left partly open for another 10 minutes, after which the xperiment re-peated.

If the baby cries the slow decrease of pressure upset and the experiment has to be stopped (Fig 5) It is seen that the slope of the high pressure cu rve is greater than the initial curve presumably because some nitrogen and oxygen will be physically absor bed in the fluid and fat tissues of the body due to the increased pressure but a correc tion for this can be made by extrapolating the curve backward to 5 min tes when the pressure was pplied Another straight line is drawn from zero t me to 5 minutes and the total pressure ncrease is the sum of these two values. After two successful experiment the baby is removed and fter due time for equilibration the volume of the chamber is measured again and hould be exactly the same as before the baby w in-troduced

Results

The density of 20 newborn infants, all below 24 hr of age has been measured The result are presented in Table 1 where it i seen that the density of a normal newborn baby varies from 0 071 to 1 083. (In these babies the gastric catheter was not inserted.)

The average value is 1 030 with a standard variation of $\pm 0\ 030$ In order to see if any relationship exists between body density and body weight a scattergram was made as shown in Fig 6 There seems to be a slight tendency to lower densities in babies weighing more than 3 5 kg but the correlation is not as clear as might be expected, if the heavier babies had a hig her proportion of fat in their bodies Nor does the density seem to vary with gesta

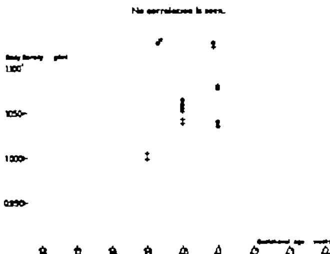


Fig. 7 The body density plotted against gestational age, but most of the observations are from full-term infants.

tional age as seen in Fig 7 but this material of normal babies includes only the period of 39 to 41 weeks, with a few exceptions. Further experiments may show higher values earlier in f tal life since the fat content of the body is known then to be lower although this may be counterbalanced by the lower mineral content

Discussion

The accuracy of th method has been estimated by measuring the volume of a dummy" consisting of two glass bottles each with a volume of 1986 ml. One bottle has in seven experiments been measured as 1980 ml ± 26 ml, and the two bottles with a volume of 39‾2 ml were measured as 3986 ml ± 51 ml in 22 experiments.

The accuracy f the method ha also been checked by measuring three stillborn infants (with no air in the lungs or gastrointestinal tract) They were measured by the hydrostatic method to have body volume of 1588 2337 and 3368 ml. In the pressure chamber the volume was determined to be 1539 2315 and 3398 respectively

When the two sets of measurements of the empty chamber carried out before and after a baby had been measured were compared in ‿3 consecutive determinations, almost equal results were obt ined, the standard deviation being 16 ml.

A weakness in this method is that a relative small volume (3000 ml) has been determined by subtracting two large volumes from each other The accuracy can therefore be increased either by decreasing the volume of the box or by pumping in more air in both cases the increase in pressure will be higher

Neither of these changes are practical. In the first case the amount of oxygen outside the baby would not be sufficient for the baby for more than a few minutes and 15 minutes seems to be the lower time limit for the experiment if precise curves

are to be drawn and too great pressure variations may be harmful to the baby

In the present set up with a volume of about 15 l of air in the closed system neither the oxygen tension will drop nor the carbondioxide increase to dangerous level during the experiment and the obtained increase in pressure is less than 1000 mm H_2O which is not harmful to the baby None of the babies have shown any signs of discomfort during the experiment except for ordinary crying without any relation to the pressure changes

The result reported here are in fairly good agreement with figures previously reported in the literature which have mostly been obtained in still-born or in dead infants.

The first figures of the density of infants was reported in 1893 by Mech [10], who found values of 1 039 and 1 044 in two dead premature babies weighing 1002 and ?03? g respectively These figures were obtained by water displacement.

Later Sytcheff [16] measured three dead premature infants and found a density of 1 0?4 1 031 and 1 035 by hydrostatic determinations.

Seitz [14] was interested in the importance of the heaviness of the head as a determining factor in the head position of the fetus *in utero* He measured 40 fetuses by water displacement and found values ranging from 1 040–1 0?5 The density of living infant was first measured by Oppenheimer [12] in 1912. He submerged 27 infant to the chin and made later a correction for the volume of the head calculated from its diameters. His figures varied from 0 040 to 1 045 with a mean of 0 99?

Kastner [8] using a similar technique measured the volume of both dead and living infants and obtained gravities, for living children, ranging from 0.883 to 1.244 and from 0.897 to 1.381 for the dead ones. The volume of 14 infant cadavers was measured by Pfaundler [13] by the above mentioned "piston-chamber" technique He obtained a mean density of 1 143 in contrast to only 0.988 obtained in the same cadavers when measured by water displacement. This difference was due to the air in the body's abdominal cavities, which on an average amounted to 404 ml or about 12.8 % of the volume of the cadavers

Barnum [1] measured the gravity of nine fetuses by suspending them in different salt solutions and observing the gravity at which they would float His results varied only from 1 040 to 1 034 except in one infant which floated in water

Similar results were obtained by Griffith [7] on 40 fetuses and still born infants by hydrostatic weighing In the 38 fresh cadavers he obtained values of 1 032 at the second month to 1 040–1 060 at 9 months of gestational age

Experiments are now in progress here where the fat content in newborn infants is estimated by simultaneous determinations of body density and total and extracellular water

Summary

A method is described by which the body density of the newborn infant can be measured in vivo. The average result obtained in ?0 newborn infants, all below 4 hrs of age is 1 030 with a standard deviation of $\pm$ 0 030

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CASE REPORT

Reticulosarcomatosis in Twins

by B. ZACHAU-CHRISTIANSEN and P A. RASMUSSEN

From the Children Hospital (Head F Tudvad M.D. Pathologist C Johansen M.D.), Fuglebakken, Copenhagen

Malignant haematological diseases in twins are extremely rare Most report [- 9 10 11 13 15] have dealt with acute leukaemia in identical twins who have succumbed to the disease in childhood often more rapidly than usual in thi di sease

In Scandinavia Wegelius & Paaso [10] have described leukaemia in a set of monozygotic twins who died about 10 month of age at an interval of 33 days.

Leukaemia has been reported also in adult identical twins [1 6 9 16]

Among approximately 500 children with leukaemia I ereen [12] found 11 twins, all discordant and several papers regarding the discordant occurrence of leukaemia in monozygotic twins and concordant as well a discordant in dizygotic twins have been published [4 9 10 17 18]

We have not been able to find any cases of reticulosarcomatosis in twins in the literature nd therefore feel that the following case report may be of interest

Case Reports[1]

Twin 4 An 11 month-old girl Admitted with d spepsia T half-siblings (aged 11 and 14 years) were in good health. The common mother now 33 years old, had always had a tendency to anaemia. During her second pregnancy she had a urinary infection, nd years later pneumonia.

In the autumn of 1959 he became pregnant; contraceptives had not been sed. Slight vaginal bleeding at the time of the first missed period and pain after 4 months of gestation. In the nd month urinary infection which yielded to sulphamethizole the onl pharmacon given during pregnancy No other d seases and no stress

In the 8th month of gestation the mother haemoglobin level wa found t be 5 .. al she w immediat ly admitted t mater n ty department and treated during the 3 week before delivery w th 3 blood transfusions (a total of 1800 ml) (All the donors were pparently health 18 month later)

Twenty days before deli ery an X ray examination pelvimetry was *done for the f rst time during the pregnancy* Presumed foetal dose 3 During the last weeks of gestation she developed mild kle oedema, which wa treated with benz flydroflumet hiazide (Centyl®) for a week.

Delivery started spontaneously and the baby w born in cephalic presentation after hours labour No sphyxia. Birth weight *00 g The infant appeared t be mature and did not exhibit any clinical abnormalities.

She wa breast-fed until the age of 3 months. Development during the first months normal. Could lift her head when prone at 3

[1] These pa ents ncluded in the 1959-1961 study on *The ym tomes f Pregnancy and Delivery in the I ant* arried out t the University Hospital, Copenhagen.

weeks, smile at 6 weeks, hold her head up at 3 months, and grab bject shortly after Thereafter she had been somewhat retarded. Could not sit without support until 9 months, gained too little in weight, but did not show actual signs of disease. Had 3 diphtheria tetanus and polio immunizations t 5 to 7 months. At the age of 10 months the infant started vomiting, developed anorexia, had thrush in the oral cavity got limp and tired, and had loose stools.

On admission, at the age of 11 months, she as lean and limp. She could stand when supported, but not alone. There was a severe moniliasis infection of the oral cavity nd X-ray examination gave rise to a suspicion that the infection had spread t the oesophagus.

Treatment was started with diet, electrolytes, and blood transfusions. Topically she was smeared with gentian violet and silver nitrate and treated orally with nystatin (a solution of Mycostatin®) Nevertheless, it proved impossible t cure the moniliasis infection, and her diarrhoea as well as vomiting continued Two weeks after admission the patient started running a temperature A urinary infection was treated with sulphamethizole but the fever persisted. Suppurative otitis was treated by paracentesis, and penicillin was administered for a time N palpable lymph nodes.

Three weeks after admission the patient began to how tremulation, but was st ll conscious, developed rigidity of the back, and became hypertonic. Treatment with benzbenzol (Peragit®) was instituted.

It was assumed that the patient must be suffering from a generalized moniliasis nfection with cerebral manifest tion, and one month after admission he wa gi en Amphotericin-B® intravenously in addition to corticoid (Actocortin®), but he went downhill, showing increasing jaundice and hepatomegaly and died few days later

Laboratory f nd ngs

Weight, 6940–6330 g Length, 0 cm. Blood. Group A_2, D neg. Hb 10.8 9.4 14.2, 11.1 g per 100 ml. Leucocy es 300, 1200, 2300 per µl, normal differential count. Platelets 63,00–17 000 per µl.

Aspiration of bone marrow showed hyperplastic leukopoiesi shifted t the l ft, presumably a sign of simple infectious affection. Blood cultures showed no growth of bacteria or fungi.

No Russian spring and summer encephalitis haemaggl tin inhibition in the serum.

ESR (micro) 5, 11 4 mm per hour Protein in serum 5.3–4.5 g per 100 ml (albumin 2.80–2.34 -glob. 0 46–0.56, α_2-glob. 0.89–0 48, β-glob. 0 46–0.55, γ-glob 0 68–0 60)

GO-transaminase, GP-transaminase, and thymol reaction elevated in the terminal stage when the prothrombin content of the blood wa 17%. Serum iron 73 and transferrin 250 µg per 100 ml. Serum calcium 4 1 and serum phosphat 2.0 mEq per l. Serum creatinine 0.62–0.50 mg per 100 ml

Spinal fl id 1–0–9 cells (mononucl) per µl. Protein 17 mg per 100 ml Glucose 60–16–60 mg per 100 ml. N growth of bacteria or fungi.

EEG: Severe diff se dysrhythmia, wit hout focal or paroxysmal bnormalities.

Urine: On one occasion leucocyturia, once traces of protein, no growth of bacteria. Normal chromatographic ppearance.

Faeces: A few times traces of blood. N pathogenic bacteria (pathogenic coli strains included) in 11 cultures, but growth of Candida albicans and Rhodotorula.

X-ray examination: Chest: Normal on admission, later a lymph node in the left hilus; screening showed no signs of subphrenic abscess. Gastro-intestinal tract; Passage normal.

ECG Normal axis, flat T waves, normal entricular complexes.

Pus from middle ear: No growth of bacteria.

Autopsy

Sparse mucous secretion in the bronchi On cut surface, the lungs showed scattered t lectatic areas. Lymph nodes up to 2 cm size were found in the hili, mediastinum, and paratracheal areas

Oesophagus of coarse calibre otherwise



Fig. 1. Photomicrograph of hepatic tissue (Twin A). General view showing perivascular cellular infiltrations.



Fig. —. High-power view showing that the infiltrations consist of reticulum sarcoma cells.

normal. Stomach and intestinal canal normal.

Liver 15 9 4 cm. On the surface and cut surface there were ill-defined greyish-red area up to 1 cm in size. Spleen 6 3 cm. Surface and cut surface as in the liver. Along the aorta there were partially confluent masses, 3 4 cm in size looking like lymph nodes.

Brain oedematous. Other organs normal.

Microscopic findings (cf. Figs. 1–3)

In the lymph nodes the lymphoid structure was obliterated, and there were widespread infiltrations of medium-sized cells with round-edged nuclei and prominent nucleoli. Cytoplasm rather ample. The splenic tissue was of the same structure.

Liver: In the periportal areas large infiltrations with similar cells, interstitially small similar infiltrations. Marked fatty degeneration, in places haemorrhages and slight tendency to necrosis.

Scattered in the brain and in several places in the leptomeninges perivascular infiltrations with cells like those found in the lymph nodes, showing nuclear polymorphism and a few mitoses.

Culture from various organs revealed gram positive diplococci in the cerebral tissue and non haemolytic streptococci in the pulmonary tissue. No growth of fungi.

Case summary

A girl aged 11 months, twin A, was admitted after failure to thrive for a few months, with vomiting and diarrhoea. She had moniliasis infection of the oral cavity and presumably also of the oesophagus. She gradually developed a septic condition with cerebral irritation, but a normal spinal fluid.



Fig. 3. High-power view showing the in asive growth of the reticulum sarcoma cells.



Fig. 4. Twin B. High power view showing that the infiltration consist of reticulum sarcoma cells.

It was not until the administration of Amphotericin B that the fungal infection yielded.

Jaundice appeared the patient deteriorated and died 5 weeks after admission. Post-mortem examination revealed diffuse reticulosarcomatosis.

Twin B

The twin sister of the former was admitted at the same time with dyspepsia.

She w born 15 minutes after Twin A. Presented by the breech, delivered by the method of Bracht. N asphyxia. Birth weight, 2900 g. One placenta, membranes torn, tw layers could not be separated. N abnormalities neonatally.

Nutrition, development and immunization as Twin A. From the age of 10 months the same *symptoms as Twin A*, but milder and without diarrhoea.

On admission pale and lean, but alert. Able to stand when supported. Running a low-grade fever and had colluria which yielded to sulphamethizole.

This twin also had a moniliasis infection of the oral cavity but it could be kept in check by gentianviolet and silver nitrat. Late however also treated with nystatin.

At the end of weeks several ttacks of a low-grade fever thought to be due t otitis media, which responded adequately to penicillin *and myringotomy*.

The left tonsil remained coated, and there was regional adenitis. Biopsy from the tonsil showed microscopic evidence of reticulosarcoma (cf. Fig. 4).

Gradually the patient developed a condition of cerebral irritation with tremor.

*After blood transfusion she was transfer*red to the Radium Centre for local irradia

tion, but died 9 days later after a total stay in hospitals of 2 months, i.e 3 weeks after Twin A She had received 3 sessions of radiation Terminally she exhibited a generalized scarlatiniform exanthema.

Laboratory findings

Weight 7410–7090 g Length, 7 cm

Blood Group A_1, D neg Hb 9 6, 10.8, 9 6 g per 100 ml. Mean corpuscular volume 60 98 mµl Mean corpuscular haemoglobin concentration *3 19 g per 100 ml. Leucocytes 6200–4800 per µl, shift to the left Platelets (terminal stage) 1_,000 per µl.

Aspiration of bone marrow showed hyperplastic leukopoiesis with a marked shift to the left and toxic characteristics as well as ample erythropoiesis shifted to the left. These findings corresponded to a non-specific presumably highly toxic action upon the bone marrow Culture from the bone marrow showed no growth

E.S R (micro) 15–31 mm per hour serum protein 7 0 g per 100 ml (albumin 3.86, α_1-glob. 0.38, α_2-glob 1 17 β-glob 0.86, γ-glob. 0.7*)

Serum iron *0 µg and serum creatinine 0 50 mg per 100 ml

Urine Leucocyturia on admission, still traces of protein, growth of E. coli. Chromatography normal.

Faeces: No growth of pathogenic bacteria (pathogenic coli strains included) Growth of Rhodotorula and Cryptococcus.

X-ray examination Chest Showed increased lung markings in the perihilar areas. Oesophagus: Normal.

Pus from the middle ears Growth of pneumococci.

Autopsy (P Meyer M D)

Some mucous, haemorrhagic secretion in the bronchi. In the lungs scattered pneumonic lesions, a few lymph nodes along the trachea and in the mediastinum.

Apart from cadaverosis of the stomach, the alimentary tract was normal No abnormality of the other organs studied The brain was not examined.

Microscopic findings

In the tonsils tumour tissue with marked nuclear polymorphism. The tissue was of mesenchymal structure with a delicately fibrillar stroma and areas of necrosis. Similar tissue in the lymph nodes and spleen. In the liver also tumour tissue with atypical, large vacuolated reticulum cells, a number of mitoses, occasional giant cells and minor anaplastic, uncharacteristic cells. In the lungs identical tumour tissue in some places quite well defined. The bone marrow showed marked hyperplasia but no tumour tissue

Case summary

Twin B a girl, aged 11 months. The twins were presumably monozygotic (cf placenta and blood group) The case history is very much like that of Twin A, only B was less debilitated on admission.

Biopsy from the tonsils showed reticulosarcoma. Despite instituted radiotherapy the infant died 2 months after admission The diagnosis was confirmed post mortem.

Discussion

According to Murphy [14] the malignant diseases of the blood in childhood comprise acute leukaemia where it may be difficult to classify the disease as myeloid, lymphoid or monocytic and chronic myeloid leukaemia which makes up only 5 % of the leukaemias in childhood, and lastly Hodgkin's disease and the lymphosarcoma–reticulosarcoma group

Danish statistics on causes of death in the age group 0–14 years indicate that the Hodgkin–sarcoma group makes up about 10 % of the malignant haematological diseases, of which 40–50 cases are seen *per annum* The incidence of leukaemia among boys and girls is 2.1 and half the cases occur in the 1st to 4th year of life Hodg

kin s disease and lymphosarcoma–reticulosarcoma in childhood occur predominantly in the age group 10 to 14 years, almost exclusively in boys

The differential diagnosis between the two diseases is hardly definite: sarcoma seems to be three times as common as Hodgkin s disease and Dargeon [7] has reported that 5% of all malignant diseases in childhood belong to the lymphosarcoma–reticulosarcoma group.

The fact that the mentioned malignant haematological diseases may occur early in the first years of life indicates that the diseases or at least the predisposition to the diseases might be congenital. The predisposition to the malignant diseases of the blood may be inherited through the maternal or paternal genes, as indicated by the definite familial occurrence of leukaemia. Future chromosomal research will possibly uncover the morphological basis. It may also be imagined that a mutation or some other cell damage (virus infection?) might occur in foetal life. In cases of concordance in identical twins such damage must have taken place in the course of the early divisions of the ovum.

In very rare cases [3 5 7] malignant haematological diseases in infants have been described as metastases of maternal disease. In our case the mother was healthy and she has later given birth to a healthy infant. The possibility of a haematogenous metastasis, via the maternal blood from the donors from whom she received transfusions shortly before the birth of the twins also seems to h ve been excluded.

It does not seem likely that the radiation dose received through the X-ray examination *shortly* before delivery can be attributed with any aetiological significance

That the twins were monozygotic was not proved on the basis of ordinary genetic principles, as we did not do an extended serological study or transplantation, but the description of the common placenta and the fact that both infants were A_2. D neg as well as their appearance indicate that they were monozygotic

Both infants had severe moniliasis twin A with dissemination to the oesophagus This is a common finding in infants with malignant diseases. The literature on moniliasis has recently been reviewed by Egeblad [8].

Summary

Reticulosarcomatosis occurred in a set of twins who are assumed to have been monozygotic. *From the age of 10 months* the patients showed lack of thriving and infections—especially moniliasis They gradually developed signs of cerebral affection, nd died t the age of approximately 13 months at an interval of 3 weeks.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Swedish Pediatric Society

Meeting Febr 8 1963

C G. Bergstrand and O Qvist Late and Early Operation of Cryptorchism

At previous follow-up studies of patients operated upon for cryptorchism the impression was gained that early operations i.e. performed before the age of 5–6 years gave a less satisfactory final result than operations made in the prepuberal years. The present investigation was made to verify this impression. During the period 1953 through 1957 operation was performed on 52 patients under six years of age With few exceptions all had an inguinal hernia which was the immediate cause of the operation. The control group consisted of patients operated during the same period at the age of 9–14 years and who had hernia diagnosed before the operation. The total number of patients was 93 of whom 88 were reexammed. In the younger age group 57 testes were operated and reexamined. The corresponding figure for the prepuberal group was 40 testes. Reoperations were made in 7 and 5 cases respectively and in these the result after the second operation was considered as the final result The period of observation varied from 1 to 9 years.

The immediate results in both groups were the same with about 90 of the testes placed in the scrotum. At the follow-up the group of patients operated before the age of 6 showed a satisfactory result in 77 %. In the rest of the patients the testicle was outside the scrotum and/or atrophied. Of the puberal group only 63 % of the 40 testicles examined were normal. The result of the investigation does not favour the impression that early operations for cryptorchism give less satisfactory results than prepuberal operations

Ulf von Euler Ingrer Larsson and Bengt Persson Glucose Tolerance in the Neonatal Period

Glucose tolerance was determined by means of an intravenous tolerance test in 6. full term children aged 5 hours to 7 days. The lowest values were obtained during the first 24 hours of life although the result remained low during the entire neonatal period and were significantly lower than in older children. Results are discussed

B Lindblad and K. Ekengren Osteomyelitis in Infants

During the years 1946–60 162 cases of osteomyelitis in children were treated at Crownprincess Lovisa Hospital for sick children, in Stockholm. Thirty five children who suffered from osteomyelitis during the first year of life were followed up by a clinical and roentgenological examination between 2 and 17 years later The good prognosis of the older children in comparison to the bad one of infants was apparent Of the 35 infants 1 showed later symptoms, 7 very slight symptoms, 4 were invalids and one had died during treatment Three of the invalids and the one who died had an osteoarthritis of the hip. The fourth invalid had an osteoarthritis of the knee All cases of osteoarthritis of the hip under four months of age led to invalidity All the older children healed without later symptoms There is a correlation between the anatomy of the vessels of the hip joint at different ages and the localisation of the inflammatory process in metaphysis and epiphysis. The 18 cases

who received heparin treatment in combination with antibiotics and surgical drainage showed the best results. There is no reason to withhold penicillin initially before the bacteriological culture report arrives. It is important to bear the disease in mind so that it should be suspected early, a puncture done and a bacteriological diagnosis made.

Yngve Larsson, Bengt Persson, Göran Sterky and Claes Thorén. Heavy Exercise in Juvenile Diabetes—Circulatory and Metabolic Observations (The "Vasalopp" Study)

Six diabetic boys and six non-diabetic controls, age 15–19 years, were studied a) *during a five months period of intense physical training*, b) at a maximal work load of 15 minutes duration, and c) during a heavy *three hours ski run, repeated for three consecutive days*. The working capacity expressed as PWC_{170} and as maximal oxygen uptake improved significantly during the training period, and the heart volume increased. In these respects the diabetics and the controls behaved in the same manner. During the short work load the FFA-concentration of plasma decreased in both groups, but immediately after work there was an increase in the FFA-level which was *more pronounced in the diabetic boys than in the controls. The mechanical efficiency* was similar in both groups. During the prolonged work a significant FFA increase occurred in the non-diabetic subjects, while there were considerable individual variation in the diabetics. The catecholamines increased identically in both groups. The average levels of serum cholesterol, phospholipids and triglycerides were somewhat lower in the diabetic boys than in the controls during the training period but within normal limits in both groups. No significant changes were *observed in these lipids*.

R. Hillberg, P. P. Hillberg and B. Blomquist. Artificial Fainting in School children

During the autumn of 196- a peculiar play behavior has been observed in some of the schools in the neighbourhood of Stockholm. The episode is described as follows: The volunteer squats, breathes deeply 10 times and then stands up quickly. *A friend* then embraces him and squeezes his chest hard for some seconds, while the volunteer stops breathing. The latter then faints and falls into the arms of his friend. Because of the possibility of dangerous sequelae this type of play was forbidden by the school physician. To study the involved physiology four pupils who had each fainted 10–20 times *were sent for a strict examination*. ECG was taken during each separate phase of the act and then during the whole experiment. The *blood pressure was also checked. It was* shown that already during the hyperventilation, the pulse was accelerated from ca 85 beat/min. to about 1-5–125. In connection with the squeezing, the blood pressure sank and the pulse rate increased to 150 just before the fainting. The volunteer then was unconscious for some seconds. On waking there was a relative bradycardia with pulse of 60–70 beats/min. With a hyperventilation alkalosis and apnoea is induced. Probably *because of this, the volunteer has no feeling of suffocation*, but on the contrary one of enjoyment. The rapid postural change, the expiration against closed glottis and the squeezing of the chest then co-operate in restricting the venous return of the right atrium. The result is a diminished diastolic filling, low cardiac output, lowered blood pressure, cerebral anaemia and fainting. The frequency of this fainting play was quite different in the different schools. One can discuss if different distribution of social groups in the three school districts in question had any significance in this respect.

Meeting March 15, 1963

The School Lunch

Panel discussion

Moderator: L. Söderhjelm

(To be published in *Svensk Läkartidningen*)

Meeting April 19 1963

J Gentz, R. Jagenburg and R. Zetterström Tyrosinosis

The clinical and laboratory findings in seven children with an inborn error of metabolism which may be defined as tyrosinosis was reported. The symptoms related to the metabolic defect are briefly as follows. Hepatomegaly has been noted rather early usually during infancy In three of the patients, the liver disease has been progressing and death from liver failure has occurred during early life. In the remaining 4 cases there has not been any marked disturbance of liver function, although the enlargement of the liver has persisted. All patients, except one who died at the age of 4 months, have developed typical Fanconi syndrome with multiple renal tubular defects causing vitamin D refractory rickets, among other symptoms. The liver surface has been nodular The structure grossly can be described as miliary postnecrotic cirrhosis with varying degree of regeneration. The disorder is inherited as an autosomal recessive gene. The seven patients belong to four different families living in a very localized area in south western Sweden. Studies of the pathogenesis have demonstrated an abnormality in tyrosine metabolism causing an accumulation of tyrosine parahydroxyphenylpyruvate p-hydroxyphenyllactate and p-hydroxyphenylacetate pointing to a complete block in the oxidation of parahydroxyphenylpyruvate to homogentisinic acid. Most likely this metabolic error causes damage to the liver and renal tubules in some way which is yet not understood. The relation between this enzymatic defect and other types of the Fanconi syndrome as well as with some earlier described cases with tyrosinosis, will be discussed.

Åke Lundberg Neonatal Asphyxia with Atrial Flutter

Neonatal asphyxia can be caused by several factors, among them different types of paroxysmal tachycardia. These arrhythmias are relatively rare may be difficult to diagnose but in most cases respond satisfactorily to digitalis. Failure to detect the arrhythmia may lead to the infant death, thereby contributing to the high mortality during the first week of life Another case of atrial flutter has recently been treated at our hospital where the question arises whether the flutter resulted in asphyxia or the arrhythmia was caused by anoxia Seen against the background of 9 previously described cases of atrial flutter among 54 cases of paroxysmal tachycardia in infancy it is concluded that the latter relationship is present in this case: 1) flutters usually show no signs of heart failure because of the low ventricular frequency due to atrioventricular block — 2) post tachycardiac ECG in this case showed none of the abnormal P waves which are often seen after severe atrial flutters in infancy Preliminary results from animal experiments shows that no P wave changes appear at these atrial frequencies until induced tachycardia has been present for 3–7 days.—The fact that the mother is an elderly primipara with an instrumental delivery is stressed. Among the above-mentioned 54 cases the percentage of mothers who were elderly primiparas was significantly greater than in normal population, a fact which is recognized among other pathological states in the neonatal period.

B. Karlsson, L. Gardeström, I Thoregren and F Jacobsson Social Adaptation of Young Adults with Cerebral Palsy

A medico-social investigation of 189 cerebral palsy patients between 16-23 years of age shows that 90 patients (48 %) have no occupation and 55 patients (28 %) are employed and managing socially Seventy of them are in institutions for mentally retarded. A more detailed study of the 119 cases who are not in institutions reveals that their employability is related to the degree of motor handicap and to the mental retardation. Patient with diplegia (paraplegia) manage best occupationally while the possibilities are considerably poorer for patients

with tetraplegia and mixed forms. The chief reasons why 20 patient ha e no occupation an severe motor handicap in 4 cases, epilepsy in 5, and mental retardation in 6 cases. Thirty patients have a markedly reduced employability and the chief reason for this is in most cases a behavior pattern characterized by inability to concentrat prolonged reaction time lack f decision and moderat mental retardation Epilepsy and motor incapacity disables only a few patient In this group. This investigation points out that intensive treatment of children with cerebral palsy ought to be followed by an intensified therapy of younger adult cerebral palsy patients.

K. Kaijser The XXXXY Syndrom

In the XXXXY syndrome there are 49 chromosomes, three of which are supernumerary X chromosomes E idence that these are se el rumosomes is demonstrated by the fact that they show the same increased DNA synthesis when labelled with isotopes (tritiumthymidine) as does one of the sex chromosomes in a normal female Moreover person with XXXXY syndrome predominantly ha three sex chromatin bodies in their cell nuclei Other characteristics of the XXXXY syndrome are extreme mental retardation and genital underdevelopment In many cases there are also kele tal malformations, strabismus and cardiac or renal abnormalities. A case of XXXXY syndrome is described. The patient was 7 years old and showed most f the typical manifestations. The parent and a younger brother re healthy

E. Norrby Gun Carlström R Lagercrantz and S Gard Vaccination with Inactivated Measles V ccine

As a primary step in analysis of the efficacy of inactivated measles vaccines, a small-scale field trial was undertaken. The vaccine used was made available by the Pfizer Research Laboratories. It was pro d ced in monkey kidney tissue cultures, inactivated with formalin and purified and concentrated by precipitation with alumi num sulphate which also acts as an adjuvant A total of 67 children aged 6 t 18 months were immunized by three monthly doses of one ml of vaccine given intramuscularly The presence of antibodies in sera collected before and 10 to 14 days after the last injection of vaccine was determined by three different techniques neutralization, hemagglutination inhibition (HI) and complement fixation (CF) tests. Among 55 children, who were fully vaccinated and not exposed to measles during the course of immunization, antibodies were detected in 54 (98%) with HI tests and in 51 (93%) with neutralization tests, whereas CF tests demonstrated con ersions in only 42 (76%) children. The serum titers reached were about half those demonstrable after a natural measles i fection Children who received only two doses of vaccine exhibited serum titers considerably lower than those with the full course of three injections. The serum t ters of children, presumably exposed to measles during the period of vaccination, were bout twice as high as those after natural infection. A similar booster effect was demonstrated in the only child of the group with pre-vaccination antibodies Further experiment have now been initiated t analyse possible advantages of the use of a concentrated and highly purified inactivated measles vaccine of a somewhat new type consisting principally of the antigen fraction which carries the hemagglutinating activities of the virus and is present in the envelope of the virus particles. This antigen stimulates the production f specific neutralizing antibodies when used for immunization of animals.

Meeting May 11 1963

C. Klackenberg Sleep Behavior in Young Children

This report comes from the prospective longitudinal growth study at the Pediatric Clinic of Karolinska Sjukhuset The author gives statistical data concerning the duration of sleeping time and frequencies of sleep disturbances at various levels up to 3 years of age Correlation—calculations show that during long periods there is some persistence in sleep behavior There are no significant differences correlated t sex, social-group, birth-order or professional status of the mothers. A group of children with disturbances of especially long duration displayed positiv correlations t vercrowding and t longcontinued breast feeding

The study will be published in *Acta Paediat* (Stockh)

Hans-Jörgen A dersen Sven P Fällström and Jan W ahberg Cow s Milk Int lerance as Cause of Malabsorbtion

Several infants with malabsorbtion, probably due to some factor in cow milk, not identical with lactose have been observed during recent years at the Pediatric Clinic in Gothenburg. Symptoms: omiting loose watery stools wasting on administration and readministration of cow milk. Symptoms disappear on breast milk feeding Steatorrhoea and low xylose absorbtion on cow milk. The malabsorbtion does not seem t be due t rapid passage At the age of 6–12 months tolerance for cow milk developed. Intolerance t large amounts of gluten appears subsequently in some cases. At the age of –3 years, these patients were normally developed as regards weight and height and had normal stools, although they had been given a regular diet, which included physiological amounts of wheat gluten.

M Böttiger S. Gard and R Lagercrantz Views on Different Poliovaccines

Between 1936 and 1956 the annual mean of registered cases of paralytic polio was 1136. Among 4 million persons who since then have been vaccinated with Swedish killed accine three cases of paralytic polio have been observed, as compared with 400 cases in non-vaccinated individuals. In 1962 total of four cases f paralytic polio were registered. N serious sideeffects were observed following more than 1 million injections of Swedish accine The campaign should continue 1) All pre-school children should be vaccinated (at present only about 70 % are vaccinated), as well as all young adult (t present about 60)) A concentrated vaccine hould be prepared for use in a quadruple-vaccine during the first six months of lif (such a vaccine would amplify the routine of vaccinations) 3) The immunity should be kept up Killed polio accine prevents paralytic polio but not contagion Individuals with high titers of humoral ant body—even if the are acquired through vaccination with killed vaccine—have relative local immunity in the gut Strains f poliovirus have relatively seldom been isolated in specimens sent to Swedish virological laboratories. N tural immunization has thus become more infrequent further reason to keep up the immunity Li e accine gives humoral as well as local immunity The former was shown by us to be satisfactory three and a half years after vaccination when persons who had received only killed accine were protected in only 70 of cases. The live vaccines are not stable and it is pos ble (though not proved) that these strains ha caused paralytic polio in man. Recently an American committee estimated the number of such cases to be 7 after 31 million accinations with type 1 and II fter 15 million vaccinations with type 3. Other viruses for instance SV 40 (which in experimental work on hamsters ha e caused tumours)—have been found in the live accine as well as in the formalinized killed vaccine Swedish plans are t continue basic immunization with killed vaccine and next year carry out a bigger field trial, administering live vaccine t individuals who have earlier received killed accine

R tger Lagercrantz, Stockholm

Acta Pædiatrica 52 631 Sept. 1963

NEW BOOK RECEIVED

Books received by the *Acta Pædiatrica* are acknowledged under this heading. Selected books will be reviewed in subsequent issues as space permits.

Year Book of Pediatrics 1962 1963 Series. Ed by S. Gellis. Year Book Medical Publishers, Chicago, Ill., 1963. Price $ 8.00

De longrat n Architectoniek ... vol bij de longontploo ng Lauweryns, Josef Arecia Ctga ren N V Brussels, Presse Académiques Européennes. 196

Morphologische Aspekt der Epilepsie Pathoge etisch Pathologisch Anatomische und Kl ische Probleme d Ep l psien. Jurgen Pfeiffer Springer Verlag, Berlin, Göttingen, Heidelberg 1963 183 pages. Price DM 48 —

Cerebellum Posture and C rebral Palsy G Walsh (Ed.) Littl Cl b Cl nics in Devel opmental Medicine No. 8. The National Spastics Society Medical Education and Information Unit in Association with W Heinemann Medical Books Ltd., London. Price 1 /6d

Intestinal Biopsy Wolstenholme G E W and Cameron, Margaret P Ciba Foundation Study Group No. 14 J & A Churchill Ltd London, 1963. Price 15s. net

Bedside Medicine Selected T p Erik Ask Upmark. Almqvist & Wiksell, Stockholm, 1963 Price Sw.kr 86 —

T berculosis in Childre E. M Lincoln & E. M Sewell McGraw Hill, London, 1963. Price £5. 0s. 6d

Prot n M tabolism An International Symposium sponsered by CIBA F Gross (ed.). Springer Verlag Berlin, Göttingen, Heidelberg 196_ Price DM 27 60

Perinatale Sterfte in Nederl nd J H de Haas-Posthuma. Two volumes. Van Gorcum, Assen. Hfl. 25. 196_

Visual Disorders and Cerebral Palsy Vernon H Smith (ed.) William Heinemann Medical Books Ltd London, 1963. Price 15 6d

BOOK REVIEWS

Cerebellum Posture and Cerebral Palsy Ed. by G Walsh.

Published by the National Spastics Society Medical Education and Information Unit in association with W Heinemann Medical Books Ltd London 1963. Price 15s.

This volume cont ins the proceedings of the International St dy Group held t Oxford in September 196_ devoted to report on recent studies in cerebellar f nction and disease The anatomy of the cerebellum is dealt with in a beautifull llustrated rticle by Brodal and it is impressive how closely this knowledge can be linked w th modern concept on it physiology as the head ganglion of the proprioceptive stem described by R shworth. Further ph siological pect on the role of the cerebellum in controlling the stretch responses, postural stabilization and in coordinating movements give information necessary for the understanding of cerebellar disorders Among the chapters devoted to diseases affecting the cerebellum the one written by Ingram on congenital at xic syndromes in cerebral

palsy must be especially mentioned as well as the excellent review by Boder and Sedgwick on the syndrome of ataxia teleangiectasia. On the whole the editor and the little club can be congratulated to this valuable contribution in making significant advances in neuroanatomy neurophysiology and neuropaediatrics available to all interested.

Bo Hellstrom Stockholm

J Peiffer Morphologische Aspekt der Epilepsien. Pathogenetische, patologisch anatomische und klinische Probleme der Epilepsien.

One hundred and eighty-five pages. Springer Verlag, Berlin, Göttingen, Heidelberg, 1963. Price DM 48.—

The author discusses central problems in the pathogenesis of epilepsy against a background of 242 brain autopsies from patients affected with epilepsy. He agrees with the view of Spielmeyer that the *majority of the* morphological changes in the horn of Ammon, such as the frequently described sclerosis, are the result and not the primary cause of the epileptic attack. The main support for this view is the close correlation between the frequency of epileptic attacks and the degree of brain damage. An angiospastic mechanism causing the injury does not seem likely however and the author points to other factors probably responsible such as cerebral edema, increased oxygen demand in the firing neurons, decreased oxygen supply to the brain by bradycardia and falling blood pressure locally predisposing factors *such as the vascular supply of the* temporal lobe and the possibility of herniation. The pathogenesis of brain damage in severe forms of epilepsy of infancy and childhood are also dealt with in greater detail and the ulegyrias, lobal scleroses and hemiatrophies are seen as consequences of fetal injuries caused by ischemia hypoxia and edema of the brain. Each section of the monograph contains an extensive and to certain extent unselected review of previous investigations. In view of the nature of the book, the number of illustrations, especiall microphotographs is limited and some of the pictures are a little difficult to interpret at least for a reader not familiar with brain pathology

Bo Hellström Stockholm

Karl Musshoff und Jürgen Wenzreich Differentialdiagnose seltener Lungenerkrankungen im Röntgenbild

Springer Verlag, Berlin, Göttingen, Heidelberg 1962. Price DM 108 —

This volume is primarily an atlas of conventional roentgenograms of the lungs illustrating rare chronic pulmonary diseases. Reasons are given for the opinion that those diseases will gain in importance with the advancement of medicine. Correct evaluation of their roentgenographic changes is then of considerable significance both for the establishment of the diagnosis and in following the course of the disease.

Classification of the different entities is based on the roentgen findings manifested mainly on a frontal picture of the chest. Differential diagnosis is discussed in introductory chapters in which reference is made to illustrated cases that have been properly selected from various clinics. Lucid legends account for pertinent clinical data and for a detailed description of the roentgen features. It is however somewhat discouraging to find that the roentgen terminology used is inaccurate. Thus, for example when describing the extent and distribution of the disease process in the lungs reference is made to upper middle and lower field instead of referring to involved lobes and segments. The illustrations are without exception of high quality and are as a rule very instructive. Most of the diseases presented belong to adulthood but there are a sufficient number of pediatric entities considered to indicate incorporation of this volume in the library of pediatric radiologist. The authors make it clear that available space does not allow full discussion of the topics concerned but relatively comprehensive list of references to mainly German literature will provide the reader with additional information.

Ulf Rudhe Stockholm

Acta Pædiatrica 52. 536. Sept. 1963

LETTER TO THE EDITOR

To The Ed tor

Beca se it seems unfortunate that misunderstandings i some places have delayed the inauguration of screening programs for phenylketonuria (PKU) in newborns I am send ng this or a similar letter to the editors of several medical journals. It occurred to me that a preliminary published note regarding the ten month experience of Massachusetts in the United States nation wide PKU newborn screening project might be of value to physicians and healt fficers of other countries especiall in countries that might be considering a screening program

In the nation wide program sponsored by the Children s Bureau using the Guthrie bacterial inhibition assay on heel blood, the Massa husetts Department of Public Health decided to go far beyond the quota assigned to the st t and in mid-J ly of 196_ offered the program to all the maternity hospitals in the st t With three cases discovered within the first four months of the program, parti cipation grew rather rapidl and by mid winter all of the maternity hospital in the stat including the mil tary hospitals with obstetrical services, were enrolled.

Although some early criticisms ha e come t our attention, in the rather large number of newborn babies that we have tested to date the blood filter paper screening test ha worked very well indeed W have not been und ly troubled with false positive reac tions, and the test has appeared quite sensitive At y rate out of 53 000 newborns tested the filter paper blood test has revealed the somewhat surprising number of 9 positives, all of which have been confirmed by serum LaDu test t independent hospitals, including in several of the cases paper chromatograms well. All of the babies were placed promptly on a low phenylalanine dietary treatment Most of the babies were detected from blood taken the fourth or fifth day before discharge from the hospital, but one phenylketonuric was detected from a blood sample drawn the third day of lif

Our result do suggest that the Guthrie screening method has real value in detecting the phenylketonuria disorder before the newborn baby leaves the hospital; this i at time when complete coverage of ll infants is virtually possible and t a time early enough for optimal treatment if a lif in an institution a a severe mental retardat is to be voided. W would therefore plead for much wider newborn screening programs in this and other countries.

Yours very sincerely
Robert A MacReady M D
Director Diagnostic Laboratories

ERRATUM

In the article of Weijers & van de Kamer in the July issue of *Acta Paediatrica* 5 3*9 Table I on page 335 has t be changed in the following way:

Acids in % of total acids instead of Acids in of wet stool" and in the column "Breastfed children the last two figures should be 2,5" and "2,5 instead of "25" and "25

Acta Paediatrica 52 537–553 Nov 1963

From the Swedish Medical Research Council Unit for Paediatric Haematology and the Department of Paediatrics University Hospital, Uppsala, Sweden.

Studies on Erythro-Kinetics in Infancy

III Disappearance from Plasma and Red Cell Uptake of Radio-Active Iron Injected Intravenously[1]

by LARS GARBY, STIG SJÖLIN and JEAN-CLAUDE VUILLE

The behaviour in the plasma of intravenously injected radioiron and its subsequent appearance in newly formed red cells is fairly well recognized in the normal adult and in patients with certain types of blood disease. Since a reasonably adequate model for ferro-erythro-kinetics has until recently been lacking [9, 18], it has not been possible to interpret quantitatively the data obtained from such studies in terms of red-cell production and destruction or in terms of iron flows and size of iron pools. However, by inference from measurements of the disappearance of radioiron from plasma in experiments designed to imitate conditions of increased and decreased red cell production and destruction and conditions of increased and decreased body iron stores [1], some qualitative information concerning these processes and states may presumably be obtained by the classical descriptive approach. The validity of such qualitative conclusions has to some extent been corroborated by comparisons with other methods of studying erythro-kinetics [2, 4, 6, 12, 22].

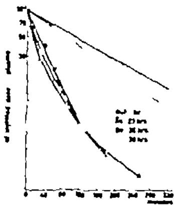
No data are available concerning the behaviour of radioiron in early infancy. The present work gives the findings in [illegible] infants aged between 0 and 931 days. These will be discussed qualitatively with respect to the changes in pattern during this age period and in adult life. Further, the data will be analysed in terms of red cell production and iron flows on the basis of the ferro-erythro-kinetic model recently proposed by Garby, Schneider, Sundquist & Vuille [9].

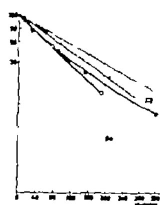
Several attempts have been made in the past to estimate the magnitude of and the changes in red cell production taking place during early infancy. These earlier estimations will be discussed in relation to the data obtained in the present work.

Material

Some clinical data concerning the [illegible] infants examined in this study are shown in Table 1. The age at the time of injection of radioiron is shown in Figs. 1–10. The haemoglobin concentration, packed red-cell volume and reticulocyte count showed all infants to be haematologically normal. Case [illegible] showed no signs of prematurity and his birth weight and calculated gestational age were normal. He had a consistently raised proportion of HbF in the blood, however, and showed an increased relative rate of

[1] This investigation was supported by grant from the Swedish Medical Research Council and by Research Contract No. 164 RB from the International Atomic Energy Agency, Vienna.





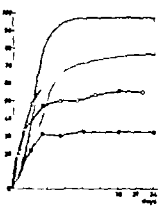
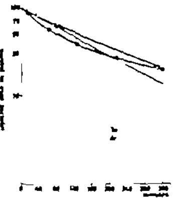
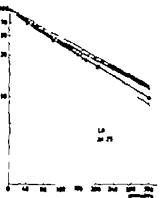
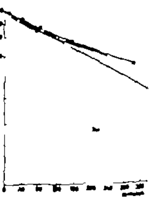
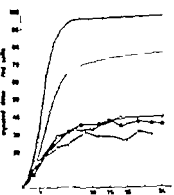
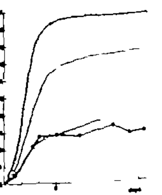
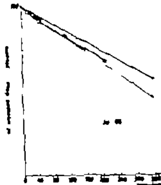
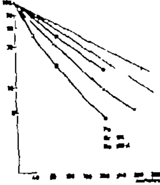



Fig 1 Fig 2. Fig 3.







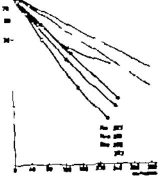




Fig. 7

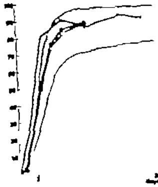


Fig. 8.

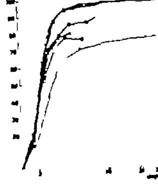


Fig. 9

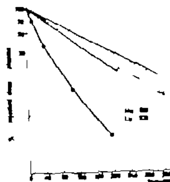


Fig. 1 10. Data concerning disappearance of plasma radioiron and appearance of red-cell radioiron. I each figure the upper diagram show the plasma data. The shaded area indicates the range (±2 S.E. for the plasma dat and ± S.D. for the red-cell data) found in normal adult (9). The age of the infant (hours or days) at the time of injection of the radioiron is also shown.



Fig. 10

TABLE 1

Material

Subject	Pregnancy: Normal	Pregnancy: Pathol.	Birth weight g	Calculated gestational age days	Delivery: Normal	Delivery: Pathol.	Condition of the infant during investigation: Healthy	Condition of the infant during investigation: Disease
Ruf	+	−	3480	281	+	−	+	−
Ås	+	−	3490	276	+	−	−	Myelomeningocele
Be	+	−	3200	27?	+	−	−	Myelomeningocele
Ni	+	−	3130	263	−	Neonatal asphyxia	−	Cerebral tumour + haematoma subdur
Run	+	−	3460	264	+	−	+	−
Ol	+	−	3120	283	+	−	−	Myelomeningocele
Ek	−	Acut. pulm. tuberculosis	4300	283	+	−	+	−
Bo	+	−	3440	280	+	−	+	−
Li	+	−	2010	235	+	−	+	−
Bl	+	−	2700	277	+	−	−	Myelomeningocele
T	+	−	3440	297	+	−	+	−
Å	+	−	3140	271	+		+	−
Sj	+	−	3210	303	+	−		−
Lö	+	−	2050	244?	−	−	+	−
J	−	Proteinuria + hypertension	3010	280?	+	−	−	Myelomeningocele
R	+	−	3910	294	+	−	+	
Bj	+	−	3890	284	+	−	+	−
J	+	−	3060	303?	+	−	−	Floppy child (+ urinary infection?)
F	+	−	4030	286	+	−	−	Convulsions
O	+	−	2710	279	+	−	+	
Ra	+	−	2710	297	+	−	+	−
N	−	Proteinuria + hypertension	3540	290	+	−		Bilateral hydronephrosis
Nie	+	−	3330	280		−		Breath-holding spells
Ste	+	−	4320	280	+	−		−
Fi	+	−	780	46	−	Caesarean section		
M	+	−	3780	280	+	−	−	Cerebral palsy
La	+	−	3890	280	+	−	−	Cerebral palsy

synthesis of HbF [10]. Case Fi had a low birth weight 2780 g, and a calculated gestational age of 246 days; he should probably be regarded as premature.

Methods

Radioactive iron (Fe^{59}) citrate in physiological saline obtained from the Radiochemical Centre, Amersham, England was injected into a scalp vein in quantities of 0.3–8.0 μC. The specific activity was about μC per μg of iron. The larger quantity (above 0.5 μC) was used in infants suffering from myelomeningocele or brain tumour.

Blood samples were taken by heel puncture, and the radioactivity in plasma and red-cells was measured as described previously by Garby, Sjölin & Vuille [10]. *Haemoglobin* was determined as oxyhaemoglobin after dilution with 0.4% ammonium hydroxide. *Blood volumes* were calculated on the basis of body weight and haematocrit value, using the relation between haematocrit and blood volume per kg body weight proposed by Mollison [14]. In the two infants with hydrocephalus, cases Ås and Ja, a correction of the body weight was made on the assumption that the blood volume is dependent only on the metabolically active

body mass. There may be some doubt whether Mollison relation is also valid for infants beyond the neonatal period; further Mollison based his relation on the venous haematocrit reading, whereas our measurements were performed on capillary blood. In the early neonatal period, capillary blood seems to give somewhat higher haematocrit values than venous blood [15 23], so that our calculations in the youngest infants may have led to slight overestimation of the blood volume. On the other hand, a comparison of the values thus btained in our infants with the figures given by others [3, 4, 17 18, 21] shows that our estimations are generally lower The calculation of blood olumes in infants may thus lead to systematic errors; moreover individual variations are probably quit large in this age group. As will be pparent from the following, however the general lack of precision in the calculated blood volumes will not materially influence the conclusions drawn in this study

Results

The results are seen in Figs. 1–10 Although there is some overlapping in the pattern, a characteristic trend in the behaviour of the radioiron can be seen Thus, at the time of birth and during the following –4 days the radioiron disappears very rapidly from the plasma. There are definit indications that the disappearance is non-linear on the semi-logarithmic plot. During the same period, the appearance of the radioiron in the red cells is also very rapid. Both processes occur t rates very much greater than those seen in normal adults. From about the fourth day onwards the disappearance from plasma is substantially lower and of the same magnitude as that seen in dults At the same time the appearance of th activity in the red cells is very slow This pattern prevails up to the age of about months, when it is again changed towards a more rapid plasma disappearance and a more rapid appearance of the radioiron in the red cells. After the age of 3 months the pattern s similar to that seen in adults, although both rates seem to be slightly greater

Discussion

The results obtained in the present study can be analysed qualitatively and quantitatively in terms of changes in the rate of red-cell production during this period of life First however some earlier work on the problem will be discussed.

Earlie work

Both theoretical and experimental analyses of erythro-kinetics during this period of lif are complicated by the fact that at no time is the circulating mass of red cells in steady state the rate of production and destruction of red cells must be assumed to be changing all the time Thus estimations of red-cell destruction (for instance by measurements of the survival of labelled cells or of the excretion rate of products from haem catabolism) which in steady state also provide information on the rate of production, can be used to assess production only if the changes in the total circulating red-cell mass are known at the same time

Three types f earlier experimental data will be discussed here since it is claimed that they supply at least qualitative information concerning the magnitude of and changes in red-cell production during the early period of life They comprise measurement of (1) the serum iron con

centration, (2) the concentration of circulating reticulocytes and their life span and (3) the concentration of red-cell precursors in the bone marrow

Vahlquist [23] found that the serum iron concentration varied characteristically during the first weeks of life After an initial rapid fall, interpreted as being due to the cutting off of the iron flow from the mother it rose from a very low level on the first day to higher values on the 6th and 14th days. These results were interpreted as indicating that the rate of red cell production decreased during the first day (or days) of life

Gairdner Marks & Roscoe [7] measured the relative reticulocyte concentration in the blood and the concentration of erythroid elements in the bone marrow in a large number of infants between birth and three months of age The relative reticulocyte concentration was high during the first 4–5 days of life (between 3–4) and then fell rapidly to about 0 8 during the following days. This low value persisted up to about two months of age when a peak value (about 2.5) was noted At the age of three months the reticulocyte concentration was again relatively low (about 0 9 %) The concentration of erythroid elements in the bone marrow followed a similar pattern except that the differences were much larger The qualitative interpretation of these data seems straightforward. they must probably be taken to mean that there is a decrease in the red-cell production during th first days after birth Subsequently a slow rate of red-cell production prevails up to about the second month of life when the production again increases The reticulocyte data can be interpreted quantitatively (1) if the relative number of reticulocytes is multiplied by the total number of circulating red cells (2) if it is assumed that the mean life span of the circulating reticulocytes is the same throughout the whole period and (3) if all the cells leaving the bone marrow do so in the reticulocyte stage The first operation introduces an unknown but probably not very large approximation The effect of the approximation introduced by assuming that the peripheral life span of the reticulocytes is constant throughout the period of investigation is not known. Künzer [13] measured the *in vitro* maturation rate of reticulocytes in cord blood and in infants between 2 to 14 weeks of age and calculated the mean cell life span from these data. There was considerable variation within and between the age groups but the figures indicate that the variation in mean reticulocyte life span during this age period probably does not amount to more than a factor of 2 Concerning the a sumption that all red cells leaving the bone marrow are in the reticulocyte stage the available data have been summarized by Seip [19] and corroborate it to some extent Very approximately then, the reticulocyte data during this period of life indicate that the rate of production of red cells decreases by a factor of 4 from the time of birth to the 4th– th day of life and possibly even more during the following days. Subsequently during the second month of life there is an increase to about 3 times the value recorded at the 4th–7th day During the third month of life there is again a fall in the production. The data concerning the concentration of erythroid elements in the bone marrow are even more difficult to analyse m

quantitative terms. If it is assumed that this parameter is directly related to the total number of erythroid elements in the bone marrow and furthermore that the rate of production of red cells is directly related to the total number of erythroid elements, it follows that the rate of red-cell production decreases by a factor of 6 from day 1 to day 4 after birth, and by a factor of 14 from day 1 to day 9

Seip [20] repeated the studies of Gairdner *et al.* on the relative reticulocyte concentration. He examined the time course of the reticulocyte values during the first week of life, and measured with great precision the relative number of circulating reticulocytes. The change in the red-cell production was calculated as indicated above from the same assumption, and Seip obtained similar results as Gairdner *et al.* Seip concluded that the rate of erythrocyte formation was approximately unchanged for the first three days of life and then fell to low values. We believe that this interpretation of his data is erroneous. The point will be discussed below Seip [20] also measured the *in vitro* rate of maturation of reticulocytes from cord blood, and found it to be similar to that of reticulocytes in dults On the assumption that the maturation rate in vitro is similar to that in vivo Seip was able to calculat the absolute magnitude of the red-cell production t th time of birth H found values between 2 4–3 0 % of the total circulating red-cell mass per day This figure is of considerable interest since it is the first well founded estimate of any erythro-kinetic parameter existing so far in this age period The estim t will be discussed further in connexion with the estimate emerging from our dat

Qualitative int rpretation of the radioiron data

The data on the behaviour of radioiron obtained in the present study are largely in accordance with the qualitative con clusions drawn from the earlier studies. Thus, the very rapid disappearance of the radioiron from the plasma and it subse quent rapid appearance in the red cells during the first days of life are compatible with a very brisk synthesis of haemoglobin, and, in fact these data can hardly be interpreted in any other way The marked change in the behaviour of the radioiron that takes place during the following –4 days is also in accordance with a very profound decrease in the rate of synthesis of haemoglobin. In fact the pattern of the radioiron appearance curves during the first month or two following the initial phase is similar to that seen in markedly hypoplastic or aplastic states in adult Between the second and third months of life the radioiron data again undergo a marked change com patible with a marked increase in the rate of ynthesis of haemoglobin. Most of the curves obtained in this period of life are also similar to those found in iron-de ficiency anaemia in adults, i a relatively rapid plasma disappearance and a shift to the left in the ppearance curve With respect to the behaviour of radioiron during this period it is notable that the reticulocyte data available [7] do not support the concept of a high rate of production of red cells after the second month of life In the study of G irdner *et al* [7], however mean values only were given on day 50 (5) and on day 80 (0 88) and it may well be that the in dividual cases beha ed a predicted by

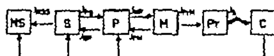


Fig. 11. The model for ferro-erythro-kinetics used in the present work. P = plasma iron pool; M = bone marrow iron pool (= exchangeable iron); Pr = precursor iron pool (= heme iron); C = circulating red-cell iron pool; S = storage iron pool, in exchange with P; NS = storage iron pool without exchange with P; J = flow of iron (mg/day) from one pool to another; the first index always indicates the pool to which the iron is flowing, the second the pool which the iron is leaving. J_s = flow of iron to pool C = measure of the rate of Hb-synthesis. $J_s = J_{Pr,M}$ if there is no intramedullar haemolysis.

our radioiron data but that there is some variation with respect to the time of onset of the increase in red-cell production.

A quantitative analysis of the radioiron data obtained during the first 10 days of life

Garby, Schneider, Sundquist & Vuille [9] have recently proposed a ferro-erythrokinetic model which seems to open new ways for the quantitative interpretation of radioiron data. In the results presented above the most striking feature is the great difference in the rates of radioiron disappearance and appearance between infants aged 1 day and infants aged 5–10 days. We thought it worthwhile to analyse the data of these two situations (Sit. I refers to age 0–1 day, Sit. II to age 5–10 days) in terms of the proposed model in order to get an idea of the quantitative changes in iron metabolism and especially haemoglobin metabolism that occur during the first weeks of life. The structure of the model considered here is shown in Fig. 11. It differs from that used in the analysis of the adult radioiron data by Garby *et al.* in one respect: the addition of the pool NS and the flow J_{NS} proved to be necessary for reasons which will be discussed later. The model is completely determined when the magnitude of the iron pools (in mg) and the iron flows (in mg/day) are known.

If radioactive iron in tracer amounts is injected into one pool (in our case pool P), the distribution of the tracer in different pools at any time after injection can be described by a set of exponential functions [9]. In these equations several parameters occur (g_1, g_2, g_3, H_1, H_2, K_1, K_2, K_3), the numerical values of which are determined by the quantitative relations between the different pools and flows [9].

In the analysis of the radioiron data we assigned to begin with more or less arbitrary values to the parameters in the exponential functions describing the concentration of the labelled iron in compartments (pools) P and C (the radioiron disappearance and appearance curves). The resulting theoretical curves were compared with the experimental curves and, in the subsequent procedure, the values for the parameters were varied successively so that finally the theoretical curves coincided with the experimental ones. Since of course the parameter values had to be identical in the disappearance and appearance function of each

individual we adopted only those parameter combinations that fitted both curves. The fitting procedure was repeated many times in each individual by using different "starting" values, so that all possible parameter combinations were taken into account From the parameter values thus obtained and the estimated iron content in pool P the magnitude of the other pool sizes and the flows (except the pools ΔS and C) could be calculated. For a full, detailed description of the analysis the reader is referred to the paper by Garby *et al.* [9]

For the fitting procedure an electronic digital computer (IBM 1620) was used, the general programme has been published elsewhere [9].

As mentioned above the magnitude of the pool P had to be estimated by an independent method We based our calculations on the figures for serum iron concentration in newborn infants given by Vahlquist [23] as direct measurements were not performed in our subjects In order to arrive at estimates for the pool size P the predicted serum-iron concentrations had to be multiplied by the predicted plasma volumes. The pool-sizes P are therefore approximate in character The degree of approximation is not critical for the purpose of this study however This will be clear from the results.

The experimental data and the curves obtained by the fitting procedure are shown in Figs. 1*–16 The corresponding parameters, the flows and pool sizes, and the rates of haemoglobin synthesis in all cases analysed in this manner are shown in Table 2.

Owing to the experimental error in the radioactivity measurements (especially in the latter part of the disappearance curve which could not be followed for a sufficiently long period) it was not possible in any infant to characterize definitely the ferro-kinetic model As a matter of fact, as seen in Tables * and Figs. 1*–16 different combinations of pools and flows satisfied the experimental data of each individual. However the flow J_{PrH} ($= J$) i.e. the estimated haemoglobin-iron synthesis flow was remarkably constant in all infants in the different matchings; moreover the values for this flow were consistent in infants of the same age (Sits. I and II respectively) The daily haemoglobin synthesis can easily be calculated from this flow Expressed in per cent of the total circulating haemoglobin, the figures are 1 1–1 6% on the first day 0 16 on day 5 and 0.06–0.08 % on days 9 and 10 (see Fig 17) Extrapolation of the curve in Fig 17 back to zero time yields a value of about 3 % per day In one infant, radioactive iron was injected immediately after birth the resulting disappearance and appearance curves followed very closely the pattern for one-day-old infants (see Fig 1). The corresponding ferrokinetic model would therefore presumably not differ significantly except for the fact that the plasma iron concentration is almost 3 times higher at birth than it is 24 hours later This means that in the hypothetical model for the infant at the time of birth, all the values for the pool sizes and the flows, as calculated for Cases Bo and Ås, must be multiplied by a factor of 3 The result thus suggests that the daily haemoglobin production amounts to about 3 of the total circulating haemoglobin at birth and falls very rapidly to about 1 5 during the first 24 hours of life In

TABLE 2 *Values for parameters, pools, flows and rate of haemoglo-*

Case	Age days	Curve no.	H	H	H	g	g	g_1	K	T
					Parameters of adapted curves					
A	1	1	0.570	0.466	0.014	93.0	28.0	1.66	0.0087	2.2
			0.570	0.464	0.014	93.0	[illegible]	1.27	0.0086	2.2
		4	0.815	0.180	0.005	60.0	16.0	0.40	0.0070	2.2
		5	0.815	0.180	0.005	60.0	10.0	0.80	0.0077	2.2
Be	1	1	0.655	0.331	0.0114	60.6	23.0	0.75	0.0001	1.8
		2	0.902	0.094	0.004	49.5	12.0	0.50	0.0036	2.1
Li	5	1	0.791	[illegible]	0.030	[illegible]	6.0	[illegible]	0.014	2.0
		2	0.843	0.155	0.0017	16.8	0.45	0.002	0.0008	2.0
T	9	1	[illegible]	0.227	0.005	18.3	0.60	0.01	0.014	2.2
		2	0.620	0.270	0.110	22.3	4.40	0.30	0.058	2.5
Ar	10	1	0.784	0.118	0.100	9.7	3.12	0.37	0.0380	1.3
			0.894	0.104	[illegible]	8.5	0.40	0.001	0.0091	1.0

TABLE 3 *Values for parameters, pools, flows and rate of haemoglobin*

The actual blood volumes are assumed to

Case	Age days	Curve no.	H	H	H	g	g	g_1	K_s	T
					Parameters of adapted curves					
Li	5		0.701	0.170	0.030	[illegible]	[illegible]	0.51	0.018	2.0
T	9		0.794	0.200	0.006	[illegible]	0.30	0.01	0.010	2.5
		4	0.620	0.270	0.110	[illegible]	4.40	0.308	0.0518	2.5

TABLE 4 *Values for parameters, pools, flows and rate of haemoglobin*

Assumption of

Case	Age days	Curve no.	H	H	H	g	g	g	K_s	T
					Parameters of adapted curves					
As	1	2	0.570	0.466	0.014	93.0	28.0	0.66	0.0086	2
		6	0.815	0.180	0.005	60.0	16.0	0.40	0.0080	2.2
Be	1		0.655	0.331	0.0114	60.6	23.0	0.73	0.0098	[illegible]
		4	0.902	0.094	0.004	49.6	12.0	0.45	0.0080	2.0

[illegible] production of the models correspond ng to the experimental curves

Pools, mg			Flows, mg/day						Rate of Hb synthesis	
P	M	S	J_{MP}	J_{PM}	J_{SP}	J_{PS}	J_{SMS}	J_{S}-J_{PSM}	mg/ day	% of THb
0.05	0.05	1.6	2.93	1.51	2.06	1.64	0.42	1.4[illegible]	416	1.[illegible]
0.05	0.06	0.9	3.29	1.45	1.72	1.07	0.65	1.83	436	1.5
0.05	0.11	2.5	[illegible].64	0.97	1.52	1.03	0.49	1.67	459	1.3
0.05	0.12	1.3	[illegible].86	0.97	1.28	0.60	0.68	1.89	534	1.6
0.06	0.06	1.3	2.30	0.62	1.54	1.19	0.35	1.65	489	1.1
0.06	0.17	1.7	2.88	0.63	1.10	0.68	0.42	1.93	574	1.3
0.16	0.07	3.3	0.68	0.46	2.06	1.61	0.53	0.22	63	0.16
0.16	1.34	87.0	1.[illegible]8	1.56	0.64	0.71	−0.06	0.22	63	0.16
0.16	0.45	10.5	2.06	1.93	0.20	0.15	0.05	0.11	32	0.[illegible]
0.16	0.13	0.9	1.33	1.20	1.0	0.65	0.2[illegible]	0.13	38	0.05
0.16	0.09	0.9	0.37	0.26	0.91	0.67	0.24	0.11	3[illegible]	0.06
0.16	0.73	48.0	0.91	0.79	0.30	0.36	−0.06	0.12	35	0.[illegible]

[illegible] production of the models corresponding to hypothet cal curves in St II

[illegible] essentially higher than the estimated ones.

Pools, mg			Flows, mg/day						Rate of Hb synthesis	
P	M	S	J_{MP}	J_{PM}	J_{SP}	J_{PS}	J_{SMS}	J_{S}-J_{PSM}	mg/ day	% of THb
0.[illegible]4	0.12	4.6	1.17	0.60	2.83	2.27	0.66	0.48	141	0.24
0.24	0.77	11.3	3.01	2.75	0.26	0.28	−0.02	0.26	77	0.11
0.24	0.20	1.3	2.10	1.80	1.[illegible]	1.29	0.[illegible]4	0.30	89	0.12

[illegible] production of the model correspond ng to hypothet cal c rves in St I

[illegible] steady state

Pools, mg			Flows, mg/day						Rate of Hb synthesis	
P	M	S	J_{MP}	J_{PM}	J_{SP}	J_{PS}	J_{SMS}	J_{S}-J_{PSM}	mg/ day	% of THb
0.05	0.06	1.4	3.25	1.51	1.78	1.69	0.09	1.74	510	1.4
0.05	1.13	1.9	3.02	0.97	1.1	1.03	0.09	2.03	601	1.7
0.05	0.07	1.1	2.54	0.6[illegible]	1.32	1.22	0.1	1.9[illegible]	543	1.3
0.05	0.18	1.4	2.82	[illegible]63	[illegible]93	[illegible]4	[illegible]11	2.19	642	1.4

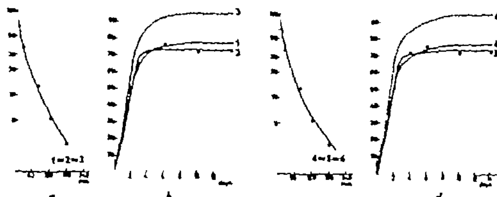


Fig. 12. Experimental radioiron dat (●) and theoretical (generated) curves in case *A* (cf. Tables and 4 for curve numbers and corresponding parameters) (*a*) Plasma radioiron data and theoretical curve no. 1 (= no = no. 3). (*b*) Red cell radioiron data and theoretical curves no. 2, no 1 and no. ... ( ) Plasma radioiron data and theoretical curve no. 4 (= no. 5 = no 6). (*d*) Red cell radioiron data and theoretical curves no. 6, no. 4 and no. 5. The ordinates denote the radioactivity in plasma (and *c*) and red cells (*b* and *d*) per cent of injected dose

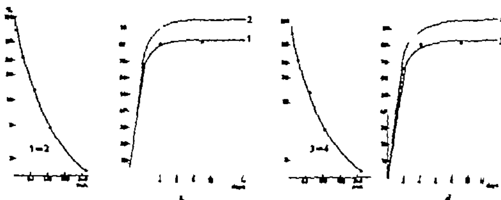


Fig 13. E perimental radioiron data (●) and theoretical (generated) curves in case *Bs* (cf. T bles 2 and 4 for curve umbers and corresponding parameters). (*a*) Plasma radioiron data and theoretical curve no. 1 (no. 2). (*b*) Red cell radioiron dat and theoretical curves no. 1 and no. 2. ( ) Plasma radioiron dat and theoretical curve no. 3 (= no 4) (*d*) Red cell radioiron data and theoretical curves no. 3 and no 4 Ordinates as in Fig 1..



Fig. 14 Experimental radioiron data (●) nd theoretical (generated) curves in case *Li* (cf Tables 2 and 3 for curve umbers and corresponding parameters). ( ) Plasma radioiron data and theoretical curve no. 1 (no 2) (*b*) Red cell radioiron data and theoretical curves no. 1 and no. 2. ( ) Plasma radioiron data and theoretical curve no 3, (*d*) Red cell radioiron data and theoretical curve no. 3. Ordinates as in Fig. 12.



Fig. 15. Experimental radioiron data (●) and theoretical (generated) curves in case T (cf. Tables 2 and 3 for curve numbers and corresponding parameters). ( ) Plasma radioiron dat and theoretical curve no. 1 (= no. 2). (b) Red cell radioiron dat and theoretical curves no. 1 and no. 2. (c) Plasma radioiron data and theoretical curve no. 3 (= no. 4). (d) Red cell radioiron data and theoretical curves no. 3 and no. 4 Ordinates as in Fig. 12

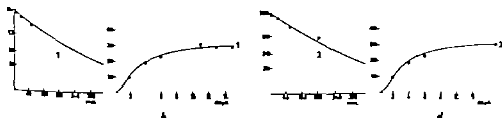


Fig. 16. Experimental radioiron data (●) and theoretical (generated) curves in case A (cf. Table 2 for curve numbers and corresponding parameters). ( ) Plasma radioiron data and theoretical curve no. 1 (b) Red cell radioiron data nd theoretical curve no 1 ( ) Plasma radioiron data and theoretical curve no. 2. (d) Red cell radioiron data and theoretical curv no. … Ordinates m Fig 12

the second week of life it is as low as 0 1%.

As to the quantitative analysis of the result the following points deserve special comment.

1 Influence of possible errors in the estimation of blood volumes and plasma iron.

2. Problem of steady state (or non steady state respectively)

3. Possible differences in the general pathway of the iron between Sit I nd Sit. II.

4 Comparison with previous work.

The basic assumptions involved in any analysis of this type have been discussed by Garby *et al* [0].

Re 1 In order to ascertain whether lack of precision in calculated blood volumes might influence significantly the conclusions concerning haemoglobin pro- d ction we adapted the appearance func tion m Cases Li and Te to hypotheti- cal curves corresponding to considerably higher blood volumes i.e 50 % higher (Figs. 14–15 dotted curves) As can be seen from Table 3 the flow *J* will be increased somewhat by thi procedure However when the daily haemoglobin production is xpressed in per cent of th total circulating haemoglobin (a figure which is perhaps more expressive than the bsolute quanti ty), the effect of a possible error in the blood volume predictions becomes quit small.

Any error in the calculation of haemoglobin production introduced by the

roughness of the figures for the plasma iron is directly proportional to any error in the latter. If the difference in plasma iron content between Sit. I and Sit. II is higher than assumed, say a factor of 3 instead of 2, the corresponding difference in haemoglobin production will still remain very great, e.g. at least a factor of 15. If on the other hand there were no increase in plasma iron at all during the first week of life, the calculated difference in haemoglobin production would exceed a factor of 40.

Re We have so far treated the data for the newborn infants as though we were dealing with a steady state. This assumption is in all probability incorrect. With respect to the ferro-kinetics, the non-steady state has different aspects in Sit. I and Sit. II.

Let us, to begin with, consider Sit. II, i.e. the age between the 5th and 10th days of life. This situation represents a non-steady state because the rate of destruction is probably much higher than the rate of production. As a consequence the circulating red-cell iron pool C is constantly decreasing and the storage pool(s) is increasing. Our mode of analysis does not allow any pool which is in direct or indirect exchange with the plasma pool to increase or decrease with time. However, the actual decrease in the pool C can be neglected since the time lag for the return of labelled iron to the plasma is much greater than the time taken by the experiment. On the other hand, the presumed increase in the storage pool forced us to introduce pool ΔS, which represents a depot to which the iron from haemoglobin breakdown is directed and from which no further exchange with plasma takes place within the time of the experiment. With this modification it will be possible to treat the central part of the model (pools S, P, M and Pr) as if it were in steady state.

The pathway of the iron return from haemoglobin disintegration needs some further comment. As yet we do not know with certainty into which compartment or compartments this iron enters. As has been discussed by Garby *et al.* [9], a return to M and/or Pr can probably be excluded in adults. The same considerations are presumably valid also for infants; thus there remain the possibilities of return to P, S or/and ΔS. Re-entrance into P yields the values for J_s and $J_{\Delta S}$ shown in Table 2. The expression $J_s + J_{\Delta S}$ (= total outflow from the central part of the model) must equal the total inflow to this part, and amounts to 0.11–1.1 mg/day in Sit. II. With an assumed daily destruction of 1–2% of the total circulating haemoglobin (see Garby, Sjölin & Vuille [11]) about –3 mg of iron would be liberated, and would have to return in our model. A quantitative return to the plasma is thus not compatible with the

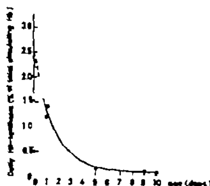


Fig. 17. The daily haemoglobin synthesis at different days after birth. The points relate to the five cases described in Table 2.

flow rate constants obtained in the fit ting procedure Return to pool S would yield somewhat larger values for J_{XS} (whereas J would remain unaltered) but even in this event the total outflow would by no means amount to 2-3 mg/day So it must be assumed that in Sit II at least *part of the iron liberated by* haemoglobin breakdown returns directly to the non-exchangeable pool VS In view of this conclusion, there are no arguments left—theoretical or experimental—to support the idea of a flow J_{XS} in Sit II, pool VS may be looked upon as being com pletely isolated from the properly kinetic part of the model. In Sit. I however a model without flow J_{XS} would generate appearance curves that would not fit the experimental data very well.

Now let us look at the problem of non steady state in Sit. I. Here there are rapid changes in the sizes of the pools (especially P) and flows (especially J) The measure ments at the beginning of the experiment do not therefore reflect the same state as the measurements at the end of the ex periment. The problem is further com plicated by the fact that the measurement of the plasma disappearance lasts for about 4 hours only whereas the appearance curve reflects processes occur ring during 1 days after injection. The changes in haemoglobin production during the interval covered by the plasma disappearance curve are so small, however that they may saf ly be neglected Be tween 1 and 3 days of life the rate of haemoglobin synthesis decreases by a factor of approximately 3 (Fig 1) and the latter part of the appearance curve there fore reflects conditions in the bone mar row distinctly different from those prevailing during the first part of the appearance curve If the rate of haemoglobin synthesis were the same on day 3 as on day 1 much more of the remaining radioactivity in the plasma would enter the bone marrow and appear in the circula tion during the following days This *means that if there were no decrease in* haemoglobin production after the in jection of the isotope the appearance curve would rise more rapidly after the second day after injection. Such hypothetical curves are shown in Figs 1 and 13 and have also been analysed mathema tically (St ll faster rates are not possible since not more than 100 of the injected *radioiron can appear in the circulation*) As can be seen from Table 4, the resulting val ues for the haemoglobin synthesis are only slightly larger than the values obtained by analysis of the experimental curves This result indicates that most of the radioiron taken up by the bone marrow has already been incorporated into red cell precursors during the first hours after injection. Thus there is good evidence that the error introduced by treating the non-steady stat as steady is not very significant

Re 3. Since the data on both Sit I and Sit II are able *to satisfy the same model* there are so far no arguments to support the idea that the general pathway of iron metabolism undergoes not only a quantitative but also a qualitative change during the first week of life except for the fact that we must assume that in Sit II a considerable part of iron liberated by haemoglobin breakdown enters directly pool VS there is no experimental evidence to suggest that this is also the case in Sit I nor are there any arguments against this

hypothesis. Theoretical considerations on Sit. II suggest the existence of a pool NS whereas the experimental data in Sit. I are in favour of the existence of a flow J_{xxx}. The most reasonable conclusion seems to be that pool NS and flow J_{xxx} reflect a real physiological mechanism occurring in both Sit. I and II.

Ad 4. As was mentioned earlier, comparison shows that our results accord closely with those of previous workers with regard to the qualitative interpretations. Quantitatively, our results would rather suggest a still greater difference between the rate of haemoglobin synthesis at birth and during the second week of life. In particular, the striking fall during the very first day (or days) of life has not been observed by other workers. This is readily understandable if we bear in mind that the radioiron method reflects the processes in the bone marrow during quite a short time interval, whereas the reticulocyte method cannot give more than average values covering several days and cannot therefore disclose very rapid changes. The persistence of a high concentration of reticulocytes in the blood during the first 3–4 days after birth reflects the output of cells rather than the actual synthesis of haemoglobin. In fact, if the data of Seip [20] are reinterpreted on the basis of considerations of the finite time required for reticulocyte maturation in the bone marrow itself, our data and Seip's become almost identical. The facts revealed concerning the very rapid decrease in haemoglobin synthesis after birth may be of importance in the study of the mechanism behind the process.

As was mentioned above, Seip [20] estimated the absolute rate of haemoglobin synthesis at birth on the assumption that the mean life span of the reticulocyte *in vivo* is identical to that *in vitro*. He found values between *4–3.0% per day of the total circulating red cell mass. Our data (Fig. 17) give almost exactly the same value. Since both methods are entirely independent and are based on quite different assumptions, the agreement is remarkable and must probably be taken to mean that both methods give valid result.

Summary

The behaviour of intravenously injected radioiron in the plasma and its subsequent appearance in newly formed red cells was investigated in 25 infants aged between 0 and 273 days and in two children aged 591 and 931 days.

The data are discussed in relation to previous studies concerning the change in red-cell production that occurs during this period of life. The data indicate a rapid and profound fall in red-cell production during the first few days after birth, and a very slow rate of haemoglobin synthesis during the following two months. Subsequently the data indicate an increased rate of red-cell production.

The data obtained during the first two weeks of life have also been analysed in terms of a recently proposed model for ferro-erythro-kinetics. The results indicate that the haemoglobin synthesis decreases at a very rapid rate (factor of 15–20) during the first 10 days of life. The absolute amount of haemoglobin synthesis at birth is between 2–3 % per day of the total circulating haemoglobin mass.

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Studies on Human Lactation

II Activities of Certain Milk Enzymes in Relation to Dietary Fat intake

by M G KARMARKAR[1] R. RAJALAKSHMI[2] and C. V RAMAKRISHNAN

Studies carried out previously in this laboratory [1] suggested a positive relation between dietary fat intake milk fat content and the activities of milk enzymes such as lipase esterase and alkaline phosphatase Subsequent studies on the effects of dietary fat supplementation on milk fat content confirmed the existence of a positive relation between the two [2]. The present paper reports data on the effects of such supplementation on certain milk enzymes viz. lipase esterase and alkaline phosphatase

Method

The samples were collected by the procedure described by Karmarkar & Ramakrishnan [1] and analysed immediately on arrival in the laboratory

The methods for the estimation of different enzymes have been already described [1]

Results

Tables 1 2 and 3 show the effects of dietary fat supplementation on the lipase, esterase and alkaline phosphatase contents of milk. It can be seen from the same that fat supplementation in the range of 25-35 g corresponding to 45 to 55 g of total intake of fat results in significant increase in the lipase esterase and alkaline phosphatase activities of breast milk. Thus these studies point to the interrelatedness of dietary fat and milk fat and the activities of certain milk enzymes, viz., lipase esterase and alkaline phosphatase.

TABLE 1 *Variation in the lipase activity of milk[a] with increasing fat supplementation.* The number of subjects was five in each group.

Fat supplement[b] per day g	Supplementation groups: Fat	Fat + protein	Fat + vitamin	Fat + protein + vitamin	Control group (No supplementation)
0	5286 ±27	5054 ±27	5064 ±27	5003 ±23	5029 +27
5	5578 ±29	5202 ±29	5110 ±28	5178 ±27	5220 ±24
15	5776 ±28	5586 ±27	5443 ±27	5460 ±26	5213 ±25
25	5909 ±28	5748 ±27	5636 ±29	5661 ±27	5205 ±25
35	5963 ±30	5745 ±30	5641 ±28	5658 ±28	5223 ±25
45	5965 ±31	5748 ±30	564 ±29	5656 ±23	5206 ±26

[a] Expressed in terms of units per 100 ml.

[b] The initial fat intake before supplementation in the subjects was 15 to 20 g/day Each level was maintained for month.

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TABLE 2. *Variation in the esterase activity of milk[a] with increasing fat supplementation*

The number of subjects was five in each group

Fat supplement per day g	Supplementation groups: Fat	Fat + protein	Fat + vitamin	Fat + protein + vitamin	Control group (No supplementation)
0	3222 ±20	3200 ±21	3149 ±22	3004 ±23	3186 ±2[illegible]
5	3444 ±22	3370 ±21	3362 ±23	3194 ±22	3176 ±24
15	3634 ±26	3485 ±23	3351 ±23	3401 ±20	3183 ±24
25	3825 ±24	3656 ±22	3701 ±24	3694 ±22	3184 ±23
35	3822 ± 4	3864 ±24	3718 ±24	3910 ±24	3186 ±24
45	3815 ±25	3660 ±25	3701 ± 3	3794 ±23	3167 ±21

Expressed in terms of units per 100 ml.
The initial fat intake before supplementation in the subjects was 15 to 20 g/day. Each level was maintained for month.

TABLE 3. *Variation in the alkaline phosphatase activity of milk[a] with increasing fat supplementation*

The number of subjects was five in each group.

Fat supplement[b] per day g	Supplementation groups: Fat	Fat + protein	Fat + vitamin	Fat + protein + vitamin	Control group (No supplementation)
0	3073 ±18	30[illegible] ±20	3092 ±21	3039 ±18	3056 ±19
5	3453 ±21	3[illegible]39 ±[illegible]0	3167 ±21	3291 ±19	3077 ±20
15	36[illegible]7 ± 1	3434 ±[illegible]	3442 ±24	3346 ±23	3064 ±[illegible]0
25	3843 ±24	3747 ± 4	3626 ±23	3615 ±21	3063 ±20
35	3937 ±24	3761 ±23	3644 ±24	3622 ±22	3063 ±19
45	3931 ±24	3765 ±24	3635 ±2	3615 ±24	3062 ± 1

Expressed in terms of units per 100 ml
[b] The initial fat intake before supplementation in the subjects was 15 to 20 g/day. Each level was maintained for month.

Discussion

It is of interest to note the presence in breast milk of enzymes which are believed to play a role in the digestion, assimilation and metabolism of fat and their relation to the fat content of milk which may perhaps contribute to some extent towards the superiority of breast milk over other foods.

The positive relation observed between fat and alkaline phosphatase contents of milk is in line with the finding reported by Stewart *et al* [3]. This study points to the existence of such a relation with regard to lipase and esterase as well, and in addition suggests that both enzyme levels and milk fat content are influenced by dietary intake. It would also appear that they are not influenced by moderate supplements of proteins and vitamins.

Summary

The activities of lipase esterase and alkaline phosphatase in breast milk were studied in relation to dietary fat supplementation.

Acknowledgement

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Studies in Oligophrenia

III Somatosexual Maturation in Mentally Deficient Children

by H. H. VAN GELDEREN and L. J. DOOREN

Introduction

Sexual maturation in adolescent mentally defectives has not been studied much. Flory [ ] found greatly retarded puberty in a large number of mentally deficient boys. Versteeg [17] noted delayed menarche in many cases of mongolism. Rundle & Sylvester [11] have shown that the testicular size of unclassifiable adolescent defectives undergoes a normal pubertal spurt. Though these authors found testicular volume of mongoloid children to be much smaller than of other mentally defectives, true hypogonadism (testes of 5 ml or less) was very rare (Sylvester & Rundle [13]).

As part of the routine examination of cases of oligophrenia in an institution for mentally defectives, we have made a study of 467 children of 9–17 years of age.

Material and Methods

The patients studied belong to the same group of children described in earlier papers [3, 4]. The few patients with hypothyreosis or hormone treatment have been excluded. No other selection was made.

From an etiological point of view the patients form a heterogeneous group. A detailed division of the patients according to the cause of mental defect would have resulted in too small numbers. Therefore we have only divided the classifiable patients into a group of children with mental defect of prenatal origin on the one hand and a group of children with brain damage of perinatal and postnatal origin on the other hand. The first group consists of patients with genetic defects, chromosomal abnormalities, embryopathy and fetopathy. Brain defects in these children are very often malformations and developmental abnormalities. In the second group mental defect may usually be considered as caused by severe damage to an originally normal brain.

Sexual maturation was measured by the usual coding method for secondary sexual characteristics (Tanner [14]). For pubic hair growth the following symbols are used:

- P: no pubic hair
- P_2: only a few pigmented hairs on the labia or at the root of the penis.
- P_3: some spread of pubic hair on the pubic mound.
- P: a tuft of some extensiveness, curled, but not yet reaching either the inguinal folds or the upper limit of the pubic mound.
- P_5: dense pubic hair reaching into the inguinal folds and the upper limit of the pubic mound (adult female).
- P: adult male.

To limit differences of coding caused by this method and to make comparison with normal values more reliable we have combined P P (no pubic hair to speak of) and P P (undoubtedly pubic hair growth).

Breast development was also coded according to Tanner [14]. Comparison with

TABLE 3 *Pubic hair in mentally deficient girls according to age.*

Age (yrs)	Mean age	Number	Percentage of girls with pubic hair stage 3 or more: Mentally defectives	Normal (Hordijk)
9	9 6	21	14	0
10	10 7	23	26	4
11	11 4	33	26	8
1	12 6	28	39	25
13	13 7	37	76	46
14	14 5	24	87	83
15	15 7	21	86	96
16	16 6	18	89	100
17	—	1	—	—
		214		

TABLE 4 *Sexual development in children with mental defect from genetic or prenatal origin (A) and with cerebral damage dating from birth or later (B)*

Percentages standardized for differences in age distribution.

Age group	A/B	Number	Puberty sign	% with puberty
			GIRLS	
9–12	A	51	Pubic hair stage 3 or more	24
	B	59		58
13–16	A	38		4
	B	31		100
9–12	A	51	Breast development stage 3 or more	24
	B	59		54
13–16	A	38		74
	B	31		94
			BOYS	
9–12	A	56	Pubic hair stage 3 or more	10
	B	63		25
13–16	A	47		55
	B	42		71
9–12	A	56	Testis size 5 ml or more	7
	B	62		21
13–16	A	47		55
	B	41		71

Significance levels for differences between group A and group B Pubic hair girls: $p < 0.01$; pubic hair boys: $p = 0.015$; breast development: $p < 0.01$; testis size: $p = 0.02$.

Table 4 demonstrates the frequency of puberty signs according to age in the patients with cerebral defects of genetic and prenatal origin compared with those of patients with cerebral damage dating from birth or later. The prenatal group matures much later than the other group: the difference is statistically significant for all maturation criteria shown.

Menstruation is often late, as can be concluded from Table 5. This is the case in the prenatal group as well as in the children with brain damage dating from birth or later. The frequency of menstruating girls among our patients is significantly lower than normal ($p < 0.01$). Menstruation therefore cannot be used as the sole indicator of sexual maturation in these institutionalized children, as will be discussed later on.

Discussion

The opinion that mentally deficient children are late maturing is a simplification. Our study indicates that *late* maturers are rather frequent, but only in the group of children with mental deficiency of prenatal and genetic origin. Only occasionally gonadal dysgenesis with abnormal sex-chromatin was found to be the cause. Usually the cause of the late appearance of puberty remains obscure.

True (persistent) hypogonadism is infrequent, as was also found by Sylvester & Rundle [13]. Most of the late maturers ultimately pass stage 3 of sexual development, as we could also conclude from follow up studies now in progress. We cannot incriminate a single group among the whole "prenatal" group: late maturers were found in mentally defectives of genetic origin as well as in mongoloid children and cases of embryopathy.

TABLE 5 *Menstruation in mentally deficient girls 9–16 years old*

Age (yrs)	Number of girls	Menstruating[a]	Expected number menstruating[b]
9	21	1	—
10	23	1	—
11	30	0	3
1	28	5	6
13	38	10	16
14	24	13	19
15	21	10	19
16	18	8	18
	210		

[a] Including three patients with secondary amenorrhea.
[b] According normal values, round numbers (van 't Land [9]).

The frequency of early maturers in girls seems also large. We have encountered at least five cases of precocious puberty in boys and nine in girls (i.e. puberty starting before the age of nine years in girls and ten years in boys). As anamnestic data about sexual maturation in our patients usually could not be obtained, more cases of precocious puberty may have been missed.

Precocious puberty is often caused by cerebral damage (Thamdrup [16]); it is therefore not surprising to find cases of early maturing in our mentally deficient patients with cerebral damage dating from birth or later. It is remarkable that damage to the brain during or after birth causing mental defect may give rise to early maturation, but apparently seldom causes late maturation. In the other mentally deficient children no cases of precocious puberty have been encountered, and early maturing is very rare among them.

Premature pubarche is occasionally found in severely brain damaged children [10, 18]. This does not influence our results, however, as breast development and testicular growth follow the curves of pubic hair development closely (Table 4). In the early maturers other puberty signs were also apparent. The same holds true for the hirsutism sometimes caused by diphantoin derivatives. Influence of drug therapy (except diphantoin) on the results of our study has been excluded after thorough analysis. As in the "perinatal-postnatal" group epilepsy is much more frequent than in the "prenatal" group diphantoin treatment was also more often instituted in the former group. Though diphantoin is thought to influence the pituitary-adrenal axis [8], true precocious puberty or early maturing has not been mentioned as far as we know.

Menstruation is a criterion of maturation which follows closely other maturation indices in normal children. In our patients, however, menstruation was often absent in girls who had matured fully in other respects, including bone-age. We cannot explain this dissociation, but we suspect institutionalization as such may be a cause, as it is in prison and camps. In our experience it is not unusual to find mentally deficient girls who have been menstruating normally at home and who show amenorrhea after having been admitted to the institution.

Other influences of the milieu upon maturation (malnutrition, chronic disease, etc.) are unlikely, as most of the patients have been in the institution for a long time and are well cared for. Besides, milieu factors cannot explain the differences in maturation rate between the children with mental defect of prenatal and those of "postnatal" origin.

Finally it should be mentioned that maturation as measured by sexual characteristics does not mean fertility: in institutionalized children fertility cannot be measured.

Summary

Four hundred and sixty-seven patients 0–17 years old in an institution for mentally deficient children have been examined for external signs of puberty. It was found that the majority of these children mature at the normal time. Late maturing is also frequent and is usually associated with mental defect of genetic and prenatal origin.

Early maturing and precocious puberty occurred only in children with brain damage dating from birth or later. These patients as a group also matured significantly earlier than children with mental defects from genetic and prenatal origin. Menstruation proved to be less reliable as a sign of maturation in institutionalized mentally defectives.

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Appendix

In statistical analysis we have used the formula $T = S / V$ in which

$$S = \sum \left(a_i - \frac{n_i r}{n_i}\right) \quad \text{and}$$

$$V = \sum \frac{n_i r}{n^2} \frac{S}{(n_i - 1)}$$

indicates one-year classes (0–17 years), a is the number of patients with puberty

signs (stage 3 or more) in one group, [illegible] the number of patients with puberty signs in the other group, S is the number of patients without puberty signs, u and v are the total number of patients in each group, and $n = u + v$. Under the hypothesis, that in the populations for every year class the fraction of patients with puberty signs is the same, the statistic u approximately follows the standard normal distribution.

An alternative method was also used, in which the year classes were combined after standardization for differences in age-composition between the groups studied. Then the usual χ^2 test of the four-square method was calculated.

Both methods gave practically identical significance levels.

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Urinary Excretion of Pyruvic Acid and Lactic Acid in Premature and Full Term Newborn Infants

by P TOIVANEN M DAHL and A. TOIVANEN

It is well known that the pyruvic acid content in the blood of premature infants is higher than that of full term newborn infants [5 15 21] The same is the case with some enzymes which are closely associated with pyruvic acid lactic acid dehydrogenase which catalyzes the reaction lactic acid pyruvic acid, and glutamic pyruvic acid transaminase which couples the metabolism of alanine to pyruvic acid [1 10 20] Moreover the prematures have an increased tendency to acidosis [4 14 17 18 24 25] which may be evidence of some anaerobiosis in prematures [17 18 24]

It would be of interest to know the further route of pyruvic acid in a non acidotic premature infant i.e to what extent pyruvic acid is broken down to water and carbon dioxide through the citric acid cycle and to what extent it has to be excreted as such, or as lactic acid. Räihä [18] has made some pyruvic acid and lactic acid determinations in the urine of four premature and three full term infants, but no conclusions are drawn in this respect Tallqvist [21] has studied the urinary excretion of pyruvic acid in 90 full term infants but his report includes no determinations in the urine of premature infants Accordingly the present study is concerned with the urinary excretion of these two acids, especially that of pyruvic acid.

Material and Methods

The daily urine output of 4 (17 male and 7 female) premature and 32 (4 male and 8 female) full term newborn infant was collected on three consecutive days by the Coloplast method The urine samples of the full term infants were taken on the first three days of life at the Maternity Hospital.[1] Other specimens were obtained from the Department of Premature Infants. At the time of investigation the premature infants were aged 1–30 days. Their birth weights were 1,50–2220 g (mean 1833 ± 50[2] g). The cause of prematurity was mild toxemia of the mother in eight cases (duration of pregnancy 236 241 244 257 250, 228, 210 and 190 days respectively) twin pregnancy in seven (duration of pregnancy 17 225, 217 225, 220 230 and 228 days respectively) abruptio placentae in one, and unknown in eight cases (duration of pregnancy 226, 220, 217 182, 194 190 198 190 and 185 days respectively). The premature infants were divided into

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[1] We thank Docent L. Rauramo, acting Professor of Obstetrics and Gynecology for permission to collect these samples.

[2] Mean error of the mean.

TABLE 1 *Pyruvic acid content in the urine of premature and full-term infants*

	Number of infants	Number of samples	Urine volume ml/24 hr	Pyruvic acid mg %	mg/24 hr	mg/24 hr/kg body weight
Premature infants						
Age 1–9 days	14	40	98 ± 6ᵃ	1.61 ± 0.15ᵃ	1.51 ± 0.10ᵃ	0.81 ± 0.09ᵃ
Age 10–30 days	10	28	122 ± 14	1.29 ± 0.12	1.35 ± 0.16	0.74 ± 0.06
Prematurity due to mild toxemia of the mother	8	23	135 ± 14	1.20 ± 0.13	1.56 ± 0.18	0.84 ± 0.09
Prematurity due to other causes	16	45	91 ± 7	1.62 ± 0.14	1.38 ± 0.16	0.75 ± 0.08
Full-term infants						
1st-day excretion	20	20	35 ± 2	3.41 ± 0.45	1.16 ± 0.12	0.32 ± 0.04
2nd-day excretion	31	31	5 ± 4	3.74 ± 0.35	1.90 ± 0.20	0.52 ± 0.06
3rd-day excretion	32	32	62 ± 5	3.52 ± 0.28	2.11 ± 0.20	0.56 ± 0.05

ᵃ Mean error of the mean.

two groups according to the cause of prematurity and to the age of the infants (Table 1 2). To the group of mild toxemia belonged children of the mothers, who had an increased blood pressure (of 140–160/90–105 mm Hg) in the last three months of pregnancy and/or proteinuria (less than 2 g/24 hr). The birth weight of the full-term infants was 2700–4820 g (mean 3486 ± 14 g). Three of the full-term infants were born by Caesarean section, and all the others, including the prematures, spontaneously per vias naturales. Infants with clinical evidence of acidosis or of other complications were not included in the material. All the infants were kept at neutral temperature"

The daily samples were acidified by adding 0.5 ml of 20 N sulphuric acid per 100 ml of urine The determinations of pyruvic acid were made using the -4-dinitrophenylhydrazine method in the form presented by Bonting [3], with the exception that the volumes used were in millilitres, and deproteinization was performed with 20 % trichloroacetic acid. For decolorization, 150 mg of Lloyd' reagent was added to _0 ml of urine The lactic acid determinations were made according t Barker & Summerson [2].

Results

The results of the pyruvic acid and lactic acid determinations are presented in Table 1–2 The differences between the values for the various groups of premature infants are statistically insignificant. The total first-day excretion of pyruvic acid in the group of full term infants is significantly lower ($0.01 > P > 0.001$) than that on the second and third day but this significance is due to the small volume of urine obtained. The lactic acid determinations are too few in number to permit comparison between the values for the separate days. The pyruvic acid excreted by premature infants aged under 10 days is 0.81 ± 0.09 mg/24 hr/kg of body weight, and the third-day excretion of full term infants 0.56 ± 0.05 The values for lactic acid are 4.75 ± 0.09 mg/24 hr/kg of body weight and 2.66 ± 0.02 respectively Both these differences between the excretion of the premature and the full-term infants are statistically almost significant ($0.05 > P > 0.02$)

TABLE 9 *Lactic acid content in the urine of premature and full-term infants*

	Number of infant	Number of samples	Urine volume ml/24 hr	Lactic acid mg %	Lactic acid mg/24 hr	Lactic acid mg/24 hr/kg body weight
Premature infants						
Age 1 9 days	7	15	104±9*	0.85±0.53*	8.62±1 46*	4 75±0.68*
Age 10–30 days		15	141±14	5.79±0.51	7 78±0.97	4.65±0.[illegible]
Full term infants		17	48±4	19.24±4 68	8.66±2.11	2.06±0.[illegible]

* Mean error of the mean.

Discussion

Although the premature and full term infants of our material were not of exactly the same age it may be concluded that premature infants excrete more pyruvic and lactic acid in the urine than do full-term infants calculated per kg of body weight This observation agrees with the high values obtained for pyruvic acid in the blood of premature infants [5 15 21] and together with the observation that premature infants excrete practically no thiamine at all [6] it may be considered a sign of the overcharge of the aerobic metabolism and the preponderance of the anaerobic metabolism The full term newborn generally excrete thiamine in considerable amounts [6] and the correlation between the high values for blood pyruvic acid and B_1-avitaminosis is well known [e.g 12 22] Räihä s observations [18] concerning the urinary excretion of pyruvic and lactic acid in four premature and three full term infants coincide with ours. Age does not influence the urinary content of these two acids in the premature infants within the age limits in the present study (Tables 1–)

Both mild and severe toxemia of late pregnancy cause a rise in the blood pyruvic acid level of the mother [7 10 11 19 23], but mild toxemia does not influence the urinary pyruvic acid content in the child, at least not more than do other causes for prematurity (Table 1)

In full term infants, Tallqvist [1] has observed a gradual decrease in the pyruvic acid concentration in urine from 12.1 mg % to 6 0 mg %, during first five days of life The total excretion tended to increase from day to day the first-day value was about 3 mg/24 hr and the fifth-day value about 5 mg/24 hr calculated from the data published in his report. The results of the present study do not clearly show the same tendency and the concentration was constant during the first three days of life The reason for the low total excretion during the first day of life is the small volume of urine obtained. This is due to part of the first-day urine often being lost in connection with delivery and to the amount of urine voided generally being small during the first day of life (e.g [21]). The values obtained by us are somewhat lower than those reported by Tallqvist but this must be attributed to the methodic difference Generally the pyruvic acid values in the present study calculated per kg of body weight, are higher than those

for adults obtained by this [13] and other methods [8 9] This may be interpreted as a peculiarity of the metabolism of newborn infants, indicating especially the great role of the anaerobic metabolism

Summary

The urinary excretion of pyruvic acid and lactic acid per kg of body weight was observed to be higher in premature than in full term newborn infants Mild toxemia of the mother did not influence the urinary pyruvic acid content in the child Both the pyruvic and the lactic acid values in urine were equally high in the two age groups of premature infants aged 1–9 days and 10–30 days

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The Relationship between Hyaline Membranes of the Newborn and the Presence of Other Pulmonary Lesions

by BENGT ROBERTSON[1]

The association between pulmonary hyaline membranes and intra-alveolar edema in the newborn has been discussed by several authors [3, 4 5, 7 8 9 10 11 1*] It has been maintained that an increase in the capillary permeability in the pulmonary circulation, possibly secondary to hypoxia, leads to exudation of edematous fluid with a high protein content, which subsequently coagulates to form membranes [9 11 12]. In a statistical analysis of the incidence of various pulmonary lesions in the newborn however no association has been found between the incidence of pulmonary hyaline membranes and intra-alveolar edema [5] but this is contrary to the findings of many other workers [4 10 11].

The frequency figures provide no impression of the intensity of the changes, and the histologic structure of the lung tissue in these cases is often diversified While one or two types of lesions may predominate in the individual case other types are often present to a lesser degree To obtain a more satisfactory impression of the histologic features account must be taken of the intensity of the lesions and the time factor

It is generally agreed that the thickness of the membranes increases with the survival time [7 10], though the opposite relationship has also been reported [6].

The incidence of different types of pulmonary lesions in cases of neonatal death has been studied previously with regard to the survival time but not to the intensity of the changes [5]. Pulmonary hyaline membranes were found to be most common during the first two postnatal days whereas intra-alveolar edema was stated to occur most frequently on the third day

The object of the present study was to examine by means of a grading system the thickness of hyaline membranes and the intensity of co-existing histologic pulmonary lesions in relation to the postnatal age of the patient.

Material and Methods

The study was performed on 117 neonatal autopsy subjects, all of which had pulmonary hyaline membranes. Since the series was derived from several hospitals no consistent clinical evaluation was possible From the available clinical data it was evident, however that all the cases had had symptoms

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TABLE 1 *Age at time of death in relation to birth weight in 117 cases of pulmonary hyaline membranes (68 males, 49 females)*

		Birth weight						
Age (hrs)	Group	< 1000	1001–1500	1501–2000	2001–2500	2501–3000	> 3000	Total
< 24	A	7	19	21	14	5	4	70
25–48	B	—	7	6	6	6	6	31
49–7	O	—	1	1	1	—	2	5
73–96	D	—	—	1	2	5	—	8
97–120	E	—	—	—	—	—	—	—
121–144	F	—	—	—	1	1	1	3
Total		7	27	29	24	17	13	117

from the first day of life, in the form either of respiratory distress (dyspnea, inter costal retractions, grunting) or of episodes of cyanosis, multiple respiratory arrest or convulsions.

The distribution of the series with respect to birth weight and age is shown in Table 1 in which the subjects are assigned to six birth weight groups, and to six age groups A–F

Specimens from more than one lung lobe were usually examined with routine stains.

Definitions Grading of the Changes

(1) *Thickness of th hyaline membranes.*—In this connection the term hyaline membrane is used in the sense of acidophil hya line substance that as seen in the sections, lines alveoli and/or lveolar duct in a band like fashion. The thickness of the



Fig 1 Grading of the histologic changes in cases of hyaline membranes. *A* Membrane thickness grade 1 in this field about 5 μ Intra-alveolar edema grade 2. Premature infant, birth weight 1480 g; death + 21 hours. Hematoxylin-eosin. 220. *B* Membrane thickness grade 2, in this field 10–15 μ. Intra-alveolar hemorrhage grade 2. Premature infant, birth weight 1310 g, death at 26 hours. Hematoxylin-eosin. 220 *C* Membrane thickness grade 3, in this field 20–23 μ Intra-alveolar hemorrhage grade 3 Full term, birth weight 2610 g; death at 4 days. Hematoxylin-eosin. 220

membranes was graded from 1 to 3 where 1 denotes thin membranes (< 10 μ), 2 moderately thick (10–20 μ) and 3 thick membranes (> 20 μ) (Fig. 1 A–C). The thickness of the membranes often varied from field to field in the individual case but an attempt was made to estimate the average thickness *from multiple measurements*.

(ii) *Intra-alveolar edema*.—The presence of opaque or slightly reticular substance in the alveoli was graded from 0 to 3, where 0 denotes the absence of edematous fluid and 3 massive pulmonary edema.

(iii) *Intra-alveolar hemorrhage*.—The presence of erythrocytes within the alveoli was graded from 0 to 3 on the same basis as edema (Fig. 1 B–C).

(iv) *Inflammation*.—Presence of intra-alveolar granulocytes, graded from 0 to 3 on the same principle as for intra-alveolar edema and hemorrhage.

The means of these four graded features were calculated for each age group.

Results

The distribution according to age enabled the appearance of the membranes to be studied, albeit in individual subjects at different times after birth. No account was taken of the influence that different forms of treatment might have had on the development of the lung changes.

As Figs. 2–5 show the thickness of the membranes and the degree of intra-alveolar edema, intra-alveolar hemorrhage and inflammation varied with postnatal age. Some reservation must be made however as regards the highest age groups which were too small to permit of reliable conclusions in this respect.

In most of the cases where death occurred during the first 24 postnatal hours (group A) the membranes were thin (< 10 μ) and there was often prominent intra-alveolar edema. In the 2–4-day groups (B–D) the membranes were generally thicker at the same time there was a gradual decrease in the intra-alveolar edema and an increase in the degree of intra-alveolar hemorrhage and inflammation. Two of the three cases in group F had very thick membranes and there was practically no intra-alveolar edema.

Statistical Analysis of the Result

The results for the membrane thickness and intra-alveolar edema were tested by the chi square method. Those represented graphically in Figs. and 3 are expressed as the means but the statistical test was based on the individual observations that is on the number of cases in the various age groups classed as 0, 1 and 2 with respect to the grade of edema and thickness of the membranes. Owing to the small number of cases in the older groups (C–F) it was necessary to combine the counts. As regards the grade of edema and thickness therefore the age groups B–F were combined, as were the edema groups 0–1 and 2–3. On the other hand, the three original classes of membrane thickness were retained.

For both edema and membrane thickness the differences between group A and the combined groups B–F were highly significant (p 0.001).

Comment

The weight and age distributions of the material are in close agreement with those previously reported. For instance Cohen et al [ ] found that 8 of the fatal cases died between and 60 hours after birth, while Claireaux [1] noted 60 % deaths for the first 4 hours. In the present material

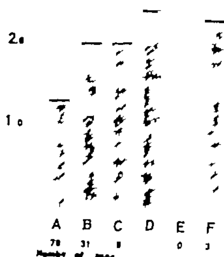


Fig 2



Fig. 3

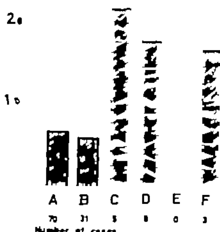


Fig 4.

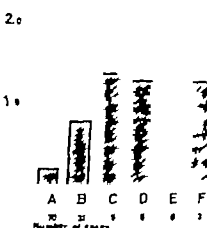


Fig 5

Figs. 2–5. Graphic representation of mean thickness of hyaline membranes, degree of intra-alveolar edema, intra-alveolar hemorrhage and inflammation in various age groups: A, 0–24 hours; B, 25–48 hours, etc.

too the relative mortality was greatest during the first 48 hours, with a total of 86 %. In Claireaux's investigation based on 108 cases of pulmonary hyaline membranes the incidence of premature births (<2500 g) was 80 %. The corresponding figure in the present study was 74 %

The male preponderance of 1.4:1 re-

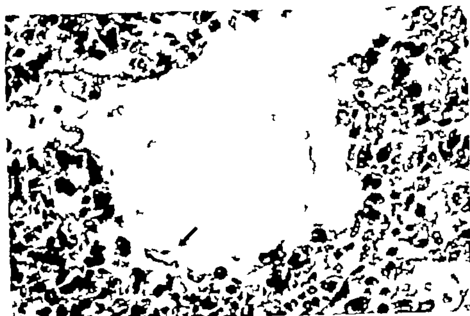


Fig. 6. Lung tissue from premature infant, birth weight 1480 g; death at 21 hours after episodes of cyanosis. Intra-alveolar edema with condensation into thin hyaline membranes (arrow). Hematoxylin-eosin. ×90.

corded in the present study is at variance with Claireaux's figure of 2.4 1

Latham [6] found an inverse relationship between the survival period and the thickness of the membranes, the cases dying early displaying remarkably thick membranes. Other workers, however, have reported the opposite relationship [7 10]. The results of the present study support the latter findings—that is to say, the thickness of the membranes increased with the survival period, at least until the fourth day of life

The fact that the membranes tended to increase in thickness inversely as the degree of intra-alveolar edema suggests that the edematous fluid condenses to form membranes. Histologic pictures suggestive of such a process of condensation are often displayed by cases dying early with prominent intra-alveolar edema (Fig 6), as has been shown by other workers [11 12].

Summary

Membrane thickness and associated histologic pulmonary changes were studied in an autopsy series of 117 neonatal deaths presenting pulmonary hyaline membranes. The ages ranged from 6 hours to 7 days. The thickness of the membranes increased with postnatal age, generally reaching a maximum on the third to fourth day. Intra-alveolar edema was prominent, especially during the first day, and diminished gradually. There was an increasing incidence of complications with age in the form of inflammation and intra-alveolar hemorrhage

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Red Cell Triiodothyronine Uptake as a Measure of Thyroid Function in Mongolism

by FRANCO SPINELLI RESSI and FEDERICO BERGONZI

In a previous publication [2] we pointed out that the *in vitro* red cell I^{131} triiodothyronine uptake (red cell T_3 uptake) described by Hamolsky *et al* [11 1?] is a test particularly useful in evaluating the thyroid status in children, because it avoids the administration of radioactive isotope to the patient.

The present paper describes the results of a study performed in a group of mongoloid children, in order to assess the applicability of the red cell T_3 uptake in determining the thyroid function in mongolism

Since it is known that the Hamolsky test is influenced by abnormalities in the pattern of serum proteins, determinations of total serum protein and protein fractions were also carried out.

Materials and Methods

Twenty five mongoloid children, ranging in age from 8 to 16 years, of whom 13 were boys and 1 girls, were studied. Twenty euthyroid, healthy children ranging in age from 7 to 12 years, and five euthyroid adult patients with liver disease served as controls.

For measuring the *in vitro* red cell uptake of I^{131} labelled triiodothyronine the Hamolsky procedure was utilized. I^{131} TRI was diluted with normal saline solution so as to contain 0 01–0 001 μg per 0 1 ml; this quantity was added, in duplicate, to 3-ml samples of whole heparinized blood in a stoppered 10-ml flask. No correction of the blood samples to a standardized hematocrit value was made before incubation. The flasks were shaken in a waterbath at 37°C for two hours. At the end of this period two 1-ml aliquots of whole blood were removed from each flask and the radioactivity counted in a well type scintillation counter The aliquots were then centrifuged, the supernatant plasma removed and the erythrocytes washed five times with isotonic saline The radioactivity remaining in the erythrocytes was then counted. The red cell T uptake was expressed as the percentage of the original radioactivity and corrected to 100% hematocrit for comparative purposes. Uptakes were expressed as an average of duplicate determinations.

In five "criss-cross" experiments carried out in order to assess the respective role of the plasma and the erythrocytes, we determined the T uptake by mixtures of normal erythrocytes in plasma from mongoloids and of erythrocytes of mongoloids in plasma from euthyroid children.

Thyroid status was determined, independently of the Hamolsky test, by clinical evaluation and basal metabolic rat

Basal metabolic rate was performed, after an overnight fast using the Benedict apparatus.

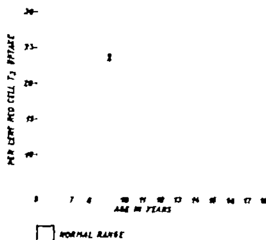


Fig 1 Red cell triiodothyronine uptake in mongoloids.

Filter paper lectrophoresis for serum protein fractions was performed using Veronal buffer at pH 8.6 and 0 05 μ.

Total serum protein wa determined using the biuret method of Weichselbaum.

Results

Tables 1 and 2 summarize the results in mongoloids and controls. In the 25 mongoloid children the red cell T_3 uptake ranged from 17 94 to *6.82 % averaging 21.33 ., ±0.5_ (S.E) No significant difference was found between boys and girls.

In the control group of 20 euthyroid children the red cell T_3 uptake ranged from 13.38 to 20.50 % averaging 10 74 % ± 0 40 (S.E) An analysis of variance showed that the difference between the two groups is significant ($P < 0\ 01$)

In the five adult patients with liver disease (cirrhosis or chronic hepatitis) associated with a demonstrable hypoalbuminemia and a decrease in total serum protein the red cell T_3 uptake ranged from 18.38 to 26 70 %, averaging 22 00 %

In seven out of 10 mongoloid children a decrease of total serum protein was found In these cases the electrophoretic determinations of protein fractions showed a decrease of albumin and an increase of gamma globulin, whereas alpha 1 alpha and beta globulins were normal.

"Criss-cross experiments, performed in five cases, showed that the uptake of normal erythrocytes *in plasma from mongoloids* was increased (mean value 22.43 %), whereas the uptake of erythrocytes from mongoloids in normal plasma was in the normal range (mean value 17.34 %)

The basal metabolic rate of all the subjects studied was within normal limits; the values of BMR in some mongoloids were in the low-normal range

Discussion

In confirmation of the findings of Kurland *et al* [15] and Jackim *et al.* [14] our studies indicate that the mean red cell T_3 uptake in mongoloid children is increased The fact that the average age of the euthyroid controls is slightly lower than that of the mongoloids cannot explain the different uptake between the two groups, since by several investigators [9 16] it has been demonstrated that the red cell T uptake in children does not differ significantly from that found in juvenile and adult euthyroid patients.

Since in previous studies [ ] we have obtained consistent results with bloods over a hematocrit range from 32 to 55 the blood samples were not corrected to a standardized hematocrit value before incubation.

According to our studies, in mongolism the Hamolsky test is not characteristic

TABLE 1 *Data on 25 mongoloid patients*

No.	Age and sex	Hct	RbcT uptake %	BMR	Total serum protein	Albumin	Globulins alpha 1	alpha-	beta	gamma
1	16 M	47	18.39	+5	—	—	—	—	—	—
2	16 M	50	22.00	+2	7.08	3.84	0.29	0.66	0.59	1.41
3	15 M	51	24.90	−1	02	3.84	0.28	0.63	0.8	1.35
4	15 M	48	20.00	+4	—	—	—	—	—	—
5	12 M	44	22.60	+2	—	—	—	—	—	—
6	14 F	43	18.37	+5	36	4.30	0.33	0.63	0.81	1.27
	12 F	41	18.02	+9	—	—	—	—	—	—
8	14 F	41	20.56	0	—	—	—	—	—	—
9	15 M	46	22.97	+1	—	—	—	—	—	—
10	9 M	47	23.03	+1	6.45	3.35	0.29	0.6	0.84	1.33
11	13 M	50	22.03	−3	—	—	—	—	—	—
12	11 F	51	24.44	+2	6.81	3.45	0.31	0.6	0.91	1.5
13	8 F	45	18.51	+5	—	—	—	—	—	—
14	13 M	50	20.96	−4	01	3.60	0.34	0.65	0.84	1.38
15	10 M	43	18.63	+7	30	4.22	0.29	0.66	0.91	1.22
16	8 M	45	26.62	+6	6.93	3.69	0.30	0.6	0.85	1.4
17	16 M	40	17.94	+1	—	—	—	—	—	—
18	10 F	41	23.41	−2	6. 4	3.5	0.33	0.6	0.87	1.40
19	13 F	44	21.06	+4	—	—	—	—	—	—
20	13 F	42	19.21	−1	—	—	—	—	—	—
21	9 F	41	20.39	+8	—	—	—	—	—	—
22	15 M	43	18.33	+3	70	4.24	0.34	0.65	1.10	1.37
23	10 F	4	22. 5	−3	—	—	—	—	—	—
24	11 F	45	19.95	+6	—	—	—	—	—	—
25	9 F	42	22.60	+2	—	—	—	—	—	—
Mean	values of controls		16.74		30	4.25	0.31	0.63	0.92	1.19

Besides the fact that as we will mention later an increased red cell T_3 uptake is found in other diseases affecting euthyroid patients, in 11 out of 25 mongoloids studied by us the uptake values fall within the normal range (Table 1 and Fig 1). However it is true that the average value of red cell T uptake in mongoloids is higher than in euthyroid patients.

Basal metabolic rate has been found normal in all the mongoloids studied by us. Besides, the most important studies of thyroid function in mongoloid children performed by means of multiple techniques, failed to reveal significant abnormalities [3 15 22] Therefore it is likely that some factor( ) other than thyroid function is responsible for the increased erythrocyte T uptake in mongolism

Jackim *et al* [14] state that the increased erythrocyte T uptake in mongolism is due to enzyme anomalies of red blood cells. No criss-cross experiments were performed by these investigators In the criss-cross" experiments performed by us, the erythrocytes from mongoloids have a normal uptake in normal plasma, whereas normal erythrocytes have an increased uptake in plasma from mongoloid patients. The same result have been observed by Kurland *et al.*

According to the explanation of the

TABLE 2 *Data on five euthyroid patients with liver disease.*

No.	Age and sex	Rbc T uptake %	Total serum protein	Albumin	Globulins alpha-1	alpha 2	beta	gamma	Diagnosis
1	60 M	26.70	6.20	2.08	0.34	0.60	0.97	1.21	Cirrhosis
2	57 M	20.37	5.60	2.82	0.31	0.63	0.91	0.88	Chronic hepatitis
3	42 M	22.91	6.90	2.63	0.29	0.59	0.90	[illegible]	Chronic hepatitis
4	72 M	21.69	6.30	[illegible]	0.33	0 71	0.91	2.13	Cirrhosis
5	58 M	23.30	5.80	1.92	0.28	0.57	0.87	2.16	Cirrhosis

mechanism of the test offered by Hamolsky the red cell T_3 uptake seems to depend mainly on the affinity of plasma for circulating thyroid hormone

Extensive studies [1 10 12 13 21] have demonstrated that thyroxine is bound in greater amount to the thyroxine-binding globulin (TBG) which migrates electrophoretically between the alpha 1 and alpha 2 globulins, and in smaller amounts to pre-albumin and albumin. Triiodothyronine is similarly bound, although less completely and less firmly and can be readily displaced by thyroxine

Therefore it may be postulated that the capacity of the erythrocytes to take up *in vitro* the added triiodothyronine depends upon the plasma thyroxine-level, i e upon the availability of binding sites. If more of the sites are occupied by thyroxine as in hyperthyroidism more of the added triiodothyronine is available for red cells The opposite would occur in hypothyroidism

Extensive studies of Crispell *et al* [4 5] have demonstrated that the uptake of thyroid hormones by the red blood cells is inhibited by plasma and to a lesser extent, by serum albumin

The mechanism of partition of T_3 between proteins and erythrocytes and the role played by red blood cells in the Hamolsky test is still not completely known. Recent studies [18 19 24] have demonstrated that erythrocytes can be replaced by resins in evaluating the thyroid function by means of a modified T_3 uptake test. Other studies [11 26] have demonstrated that modification of plasma proteins can affect the red cell T_3 uptake Euthyroid patients with liver disease nephrosis or malignancy in which total protein is decreased because of a decrease of albumin, show an increased erythrocyte T_3 uptake As shown in Table 2 our studies on five patients confirms the increased red cell T_3 uptake in liver disease associated with hypoalbuminemia Also the low red blood cell T uptake in pregnancy is most likely due to a plasma factor [17]

The studies of several authors [23 25] and particularly those of Nelson [20] on about 200 mongoloids have demonstrated in mongolism a decrease of total serum protein due to a decrease of albumin. The level of gamma globulin was found significantly increased, whereas no significant differences over controls were demonstrated in alpha 1 alpha 2 and beta globulins.

The studies of plasma of mongoloid children performed by us demonstrate in seven cases the same anomalies of plasma

proteins mentioned above. In all these cases an increased red cell T uptake was found.

These findings, and the results of "criss-cross" experiments, would indicate that in explaining the increased red cell T_3 uptake in mongolism, the role played by plasma cannot be ignored.

The electrophoretic picture of proteins binding thyroid hormones in those mongoloids in which anomalies of plasma proteins are found is similar to that found in euthyroid patients with liver disease in which the erythrocyte T uptake is increased.

It is beyond the purpose of this paper to demonstrate which plasma factor(s) is possibly responsible for the increased erythrocyte T_3 uptake in mongolism. It should be noted that, among plasma proteins known to bind thyroid hormones only albumin is quantitatively affected in mongolism, whereas alpha 1 and alpha globulins are normal. However it should be pointed out that, even if all the mongoloids with abnormalities of serum protein studied by us have an increased red cell T_3 uptake a strict correlation between increase of T uptake and decrease of total protein and albumin could not be demonstrated by our studies.

We are not able to say if the enzyme anomalies of red blood cells in mongolism described by J ekim *et al* [14] are in part responsible for the increased T_3 uptake However it seems to us that no evidence has been given by these authors that erythrocytes from mongoloids behave differently as far as the Hamolsky test is concerned, from those of non mongoloid subjects.

In any case whatever the extrathyroid factor(s) which influences the red cell T uptake is it appears from our studies that the test described by Hamolsky is not a valuable tool in assessing the thyroid function in mongolism

Summary

The red cell triiodothyronine uptake was performed in a group of 25 mongoloid children, in order to assess the applicability of this method in evaluating the thyroid status in mongolism. Our studies indicate that the mean T uptake in mongoloids is increased However in 11 out of 25 mongoloids studied by us the uptake values fall within the normal range so that the test cannot be considered characteristic in mongolism In all the mongoloid children the BMR was normal. On the contrary in seven cases with an increased red cell T uptake a decrease of total serum protein and albumin was found. Since it is known that abnormalities of plasma proteins influence the red cell T_3 uptake the hypothesis that some plasma f ctor( ) is responsible for the increased uptake of labelled triiodothyronine in mongolism is suggested. Whatever the extrathyroid factor(s) responsible for the increased red cell T uptake is the technique is not a valuable tool in assessing the thyroid function in mongolism

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Hereditary Nephropathy with Haematuria

by NIELS HOBOLTH

Familial nephropathy simulating glomerulonephritis seems to have been reported for the first time in 1874 by Samuelson [28] in Germany and in 1875 by Dickinson [7] in England. Apart from the 35 families [2 4–6 9 11–19 21–27 29–31] reported in the last decade only a few families with a typical inheritance and clinical picture are on record. According to the suggestion of Williamson [32] the disease which is often inherited in association with perceptive deafness, should be referred to as Alport's syndrome [1] This syndrome comprises an incomplete sex linked, dominantly inherited nephropathy whose main and earliest sign is a varying degree of haematuria, frequently albuminuria, and at times casts and leukocyturia The symptoms are intensified by infectious diseases and pregnancy Affected males develop uraemia as a rule before their 30th year of age while in females the length of life is not influenced to the same extent, and they seldom develop uraemia In some families the nephropathy is associated with perceptive deafness [4, 5 9 11 13, 16, 19 22, 23, 25 26 29 30 32] which usually manifests itself in the second decade of life The hearing loss may also occur in individuals who are not suffering from hereditary nephropathy (h n) [1 30] and reversely all members of the named families with h.n. need not have impaired hearing In some families there have been cases of ocular defects, especially affecting the lens [11 25 29 32]

Pathological studies on the renal disorder have been carried out partly on biopsies [4 17 22, 23] and partly on autopsy specimens [4, 5 6 9 11 13 16 19 22 23 26] The organic renal changes appear to develop gradually so that initially the ordinary light microscope does not reveal any abnormalities, either of the nephrons or of the interstitial tissue [4 22] When the disease has persisted for a long time there will be incipient epithelial crescents in the glomeruli, interstitial fibrosis [5 22], or sclerosis of juxtaglomerular vessels [17].

Patients who have died of the disease show on gross inspection contracted kidneys with a granular surface Some authors have found yellowish, patched areas, showing on cut surface yellowish radial streaking consisting of phagocytes with a lipid content [4 11 23] The cortical and medullary zones show varying degrees of

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Read, in a somewhat modified form, before the meeting of the Danish Paediatric Society on Nov 14, 1962.

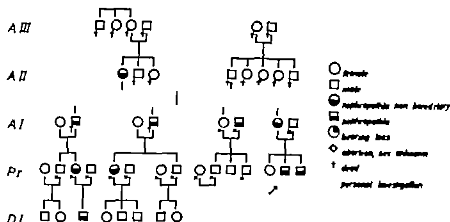


Fig 1 Family I Pedigree with explanation of symbols.

contraction. The histological findings have consisted in varying degrees of fibrosis and hyalinization, epithelial crescents in the glomeruli and periglomerular fibrosis [4 5 9 11 13 22] The reported tubular changes have varied within wide limits. The most severe lesions are said to affect the proximal tubes [23] In the interstitial tissue there will be varying cellularity and increased connective tissue In some families the inflammatory changes predominate the appearances reminding most of all of chronic pyelonephritis [11 22 23] In others, glomerular and fibrotic changes are most outstanding so that the picture is similar to chronic glomerulonephritis or interstitial nephritis [4 5 13 16 19 .. 27]

There has been only one report on an autopsy of the inner ear in a patient with inherited hypacusis. No characteristic changes were found [22]

The ordinary treatment of nephritis has been tried but there has been no beneficial effect of a low-salt diet prolonged bed rest [13 22] antibiotic therapy [18] or adrenocortical steroids [2, 6 17 25 27].

Present Investigations

In our department we have had some members of two families in which h.n. is inherited.

All the accessible records on all members of these families were perused in order to appraise urinary findings, renal function, abnormal pregnancies, and hearing In addition, all living members were examined personally whenever permitted by geographical distances and the persons willingness to co-operate Microscopic examination of the urine was always performed on freshly and spontaneously voided urine Only those cases in which the author personally performed the microscopic examination of the urine are marked "personal investigation" in Fig 1 and ..

Whenever the interview gave rise to a suspicion of hearing loss, audiometry was carried out Furthermore audiometric screening was done on all the members of Family II who were old enough to cooperate Only audiologically confirmed hearing loss was recorded in Fig

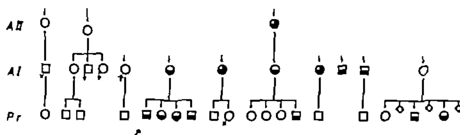


Fig. 2. Family II. Pedigree. Symbols: see Fig. 1

Case Histories

Family I

This family comprises 22 descendants over three generations of a woman who must have had h.n. (Fig. 1). Among these descendants there were eight cases of h.n. (Table 1). The following are of particular interest.

AII 1:—An 62-year-old woman who had undergone several operations for cataract. Shortly before her death from cerebral thrombosis, she was found to have erythrocyturia and leukocyturia + bacteriuria, serum creatinine 1.5 mg/100 ml. At autopsy the kidneys were found to measure 11 6 4 cm. The capsules were easily detached, and the surface showed a delicate uniform granulation. In the left kidney there were infarcts in the upper and lower poles. The parenchyma, especially the cortex, was somewhat narrowed. Microscopic examination revealed a largely well-preserved renal parenchyma with scattered hyalinized glomeruli. In the pyramids there was a fairly marked increase in the interstitial connective tissue which was hyalinized. Moreover there was thickening of the medium-sized and major arterial branches with narrowing of their lumina. No data were available regarding her pregnancies, and records from previous admissions to hospital were non-contributory regarding microscopic examination of the urine. A single investigation for albumin had been negative.

AI 1:—Rejected for military service at the age of 18 because of chronic renal disease. Led an active life until a few months before dying at the age of 36 in a state of uraemia. No autopsy report.

AI 2:—Led an active life until a few months before dying at the age of 43 in a state of uraemia. No autopsy report.

Pr 9 Proband:—A 10-year-old boy whose development had been normal. In a routine study at the age 16 haematuria was detected.

TABLE 1. *Family I. Abnormal laboratory findings*

Persons showing normal results are not included in the table

Generation	Number	Sex	Age in years († at death)	Albuminuria in pregnancy	Hearing loss	Eye defect	Urinalysis: Albumin	Glucose	Leucocytes	Erythrocytes	Casts
AII	1	F	†62	?			+		+	+	
AI	1	M	†36		?				+	+	+ Uraemia
	2	M	†43						+	+	+ Uraemia
	4	F	43							+	
Pr		F	27							+	
	3	F	20						+	+	
	9	M	16							+	+
	10	M	8							+	+
DI	3	M	3							+	+

TABLE 2 *Family II (cf legend to Table I)*

Generation	Number	Sex	Age in years	Albuminuria in pregnancy	Hearing loss	Eye defect	Urinalysis: Albumin	Urinalysis: Glucose	Urinalysis: Leucocytes	Urinalysis: Erythrocytes	Urinalysis: Casts	
AII	3	F	61	+	+							
AI	6	F	36	+					+		+	
	7	F	34		+							Nonhereditary nephrolithiasis
	8	F	33	+			+		+	+	+	
	9	F	31	+	+		+			+		
	10	M	30		?					+		
	11	M	27		?		+			+	+	
Pr	5	M	17			+	+		+	+		
	6	F	12							+		
	7	F	10							+		
	8	M	8							+		
	14	M	4							+	+	
	18	M	4						+	+		
	19	F	1						+			Nonhereditary

Since that time all investigations have shown varying degrees of haematuria, at times albuminuria. The symptoms were aggravated by throat infections. On admission there were no striking findings apart from the persistent haematuria. No other abnormal bleeding tendencies, a normal BP normal ophthalmoscopic appearances, normal audiogram. The renal function, assessed by blood urea, creatinine and clearance, was normal. I.v pyelography showed normal renal shadows and normal pyelograms.

Pr 10—The patient's younger brother was also normally developed. At the ge f 3 years he was admitted t the department with albuminuria and haematuria, but there were no clinical abnormalities. ESR 21 mm/hour Total serum protein 6.5 g/100 ml. Paper lectrophoresis α_2 globulin 12.6%, other fractions normal. The condition did not change on penicillin and prolonged bed rest. On re-admission at the age of 7 the patient was feeling well. His urine was still abnormal and so was the distribution f the serum protein fract ons. Renal function normal assessed by blood urea, creatinine, and clearance test. Slightly elevated total cholesterol. I.v pyelography showed normal renal shadows and normal pyelograms.

The spouse f *AI 3* was in good health, but in the course of this family study he was found to have albuminuria, erythrocyturia, and leukocyturia. His renal disease has not been investigated in more detail, but it is probably not inherited.

Family II

The second family comprises three generations. Among 23 descendants of a woman having h.n. and hearing loss (Fig. 2) there were 14 cases of renal disease (T ble 2) The cases of most interest are as follows.

AI 7—A woman with hearing impairment of the perceptive type. No data regarding recurrent otitis media. History of an operation for nephrolithiasis. N other renal diseases and apparently not h.n.

Pr 19—Pyuria, but no haematuria when first seen. After sulpha drug therapy the urine was complet ly normal. She is probably not suffering from h.n.

AII 3 and AI 9—Both these members have hearing impairment of the combined conduction and inner-ear type. Both had a history of numerous episodes of purulent otitis media, which might explain the hearing impairment, but an inherited factor cannot be excluded.

Pr 5 Proband—Admitted to the depart ment at the age f 9 years. Even then, he had

TABLE 3. *Fractionated urinary protein excretion in three boys with manifest proteinuria caused by inherited nephropathy compared with the corresponding serum values*

		Total g/l	Albumin	Globulin alpha	Globulin beta	Globulin gamma	Heat precipitation C
Fam. I Pr 9	Urine	0.21	57	16	1	10	79
	Serum	*66*	*57.6*	*14.0*	*10.4*	*16.0*	
Fam. I Pr 10	Urine	0.27	64	21			63
	Serum	*66*	*51.4*	*20.1*	*10.1*	*17.4*	
Fam. II Pr 3	Urine	0.23	77	14	5	4	84
	Serum	*69*	*53.6*	*16.5*	*10.3*	*14.0*	

been admitted several times to other departments with haematuria which had been diagnosed at the age of 5 years. We found no abnormal bleeding tendency apart from haematuria. There was albuminuria, erythrocyturia, and [illegible] times leukocyturia. I.v. pyelography revealed normal pyelograms and normal renal shadows. There had always been microscopic haematuria, and at times also gross. The patient is myopic. Spherofakia has not been diagnosed.

AI 11.—Admitted several times to other departments but albuminuria had not been found there. This person was not examined by the author personally.

Special Investigations

All the living adult members and most of the children of Family I were investigated for autoantibody to renal tissue using precipitation by diffusion in gel according to the Ouchterlony principle [20], haemagglutination by the Boyden principle [2], and complement fixation reaction by the Donelley semimicromethod [8]. Autoantibody to renal tissue could not be demonstrated by these methods. The same sera were investigated by immunoelectrophoresis, but did not show changes that might be called characteristic of this disease. Paper electrophoresis of the serum proteins showed, as a general rule, normal or low albumin and high or normal α_2-globulin. Other fractions, in particular the γ-globulin, were normal.

Carried out by Dr. Tage Hjorth, Institute of General Pathology, Aarhus.

The urinary protein fractions were studied in Pr. 9 and Pr. 10 of Family I and Pr. 5 of Family II. The excretion pattern indicated nephropathy with increased glomerular permeability. There was strikingly high excretion of [illegible] globulin, suggestive of the appearances in nephrosis (Table 3).

Tubular function was investigated in Pr. 9 and Pr. 10 of Family I. This showed a normal concentration ability, normal excretion of amino acids, and a normal re-absorption of phosphate (determined by the method advocated by Friis [10]).

Discussion

The very prolonged, and as far as the females are concerned very mild, syndrome in the present material as well as the nature of the symptoms and signs, haematuria and albuminuria combined with the typical heredity establish the diagnosis of h.n. of the type reported in the literature. Family II also included several cases of hearing impairment which justifies the classification of the condition as Alport syndrome as suggested by Williamson. The presence of hearing loss in one member of the family without h.n. is in accordance with several reported cases [1, 30].

Carried out by Dr. Birthe Tidstrøm, Protein Laboratory, Institute of General Pathology, Copenhagen.

In Family II there was a history of frequently recurring pyuria. Thus the syndrome in this family is very like that described by a smaller group of authors [11 16 18 22 23 26] The tendency to pyuria appears to be a characteristic of these families and as it comprises several generations it is difficult to explain merely as a result of environmental factors.

The biopsy findings indicate that the very widespread changes found in the kidneys of patients who have died of hn are secondary to a primary lesion whose character *is unknown except for the fact* that it is hereditary Presumably it is a glomerular lesion This is suggested by the haematuria which is the first and only sign in the young patients. The youngest patient with confirmed haematuria who is on record was 10 days of age [17]. Moreover the first changes observed in the light microscope are localized in the glomeruli and it has not been until a late stage of the disease that these patients have shown tubular dysfunction [11] However Nieth [19] found renal glucosuria without other signs of tubular dysfunction in a female patient

Since the clinical picture and the histological findings may be reminiscent in many ways of the experimentally induced glomerular injuries in the Masugi kidney investigations for autoantibody to renal tissue were performed in Family I but without positive findings.

Just as in renal diabetes insipidus the disease gene is attached to an X chromosome. The result is—in addition to the typical mode of inheritance—that the disease manifests itself in a more severe form in males.

The diagnosis of these particular renal diseases is based not only on the clinical signs but also upon the demonstration of the hereditary factor The latter is apt to be overlooked, as the symptoms are so mild in the females. Especially among the younger age groups the disease may often be mistaken for acute glomerulonephritis. In the case of the boys, this will make us liable to expect the prognosis of acute glomerulonephritis to be poorer than it is in actual fact.

It is striking that several authors [5 21 25 30 32] have been able to publish two or three *families*, one even six *[2] living* within a limited geographical area. This fact together with the difficulty in differentiating the disease from acute glomerulonephritis, makes it probable that the paucity of the published family studies indicates rather that the disease is apt to be overlooked than that it is extremely rare

Summary

This is a study of two families having an inherited nephropathy manifesting itself in childhood by haematuria and in some cases albuminuria with or without hearing loss—a disease which has previously been described as Alport s syndrome.

The first family comprises 23 descendants over three generations of a woman who has probably had hereditary nephropathy Eight members had the renal disease Two males had died in uraemia The mode of inheritance was typically sex linked dominant There was no case of hearing loss. The second family comprised three generations. Among 23 descendants of a woman having hereditary nephropathy and hearing loss there were 11 cases

of hereditary nephropathy and two cases of hearing loss. The inheritance was domi nant. Sex linked inheritance was possible

Especially in children the disease is apt to be misdiagnosed as acute glomerulonephritis. As th symptoms are mild in females, a special search has to be made for the heredity

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The Incidence of Infantile Hydrocephalus in Sweden

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A growing clinical interest in the true incidence of infantile hydrocephalus (i.e hydrocephalus of the expansive type) has developed during recent years due to an increased surgical activity parallel to im proved shunt procedures Earlier studies mainly refer to hydrocephalus present at birth and regarded as a malformation However figures for clinical use must also include all cases starting later in infancy The majority of these belong to the group of so called simple" hydrocephalus which should be distinguished from those combined with *spina bifida cystica*. Stu dies on newborns give an erroneously low incidence and tend to exclude a number of prognostically favorable cases. On the other hand, in a retrospective field study cases of *spina bifida cystica* with hydroce-phalus are easily missed as at death they are apt to be registered only as myelo-meningoceles.—The true incidence can best be obtained from combined studies covering the whole period of infancy In addition, the incidence rate is not com parable from one country to another as large geographical differences exist [12].

The aim of the present retrospective study is to give figures as close as possible to the true incidence of infantile hydro-cephalus in a Swedish population and be-ginning before the end of the first year of life. For this reason two separate studies have been performed

Study A The number of cases present at birth was determined in a material from an obstetric clinic. Special attention was paid to hydrocephalus combined with *spina bifida cystica*.

Study B The number of cases devel-oping during the first year of life was examined in a field study where special emphasis was put on cases of "simple hydrocephalus without complicating *spina bifida cystica*

Material and methods

Study A The clinical material refers t the 43,548 registered births at the Department of Obstetrics, University Hospital, Uppsala, between the years 1944 1961 The records of all infants with malformations of the central nervous system noted at birth ha e been studied. Most of these cases had also been cared for in the Department of Pe-diatrics and the case histories, as well as post mortem records of dead cases were studied. The total number of deliveries and the number of live births during the period, and the birth weights within the actual group were recorded. Cases from the mate-rial not registered as hydrocephalus at birth but found t have this disorder during the first few weeks of lif were included as

TABLE 1 *Anatomic defects of the central nervous system at birth A survey of 43,548 total births or 42,779 live births at the Department of Obstetrics University Hospital Uppsala during 1944–1961*

	At birth							
	dead		alive					
	♂	♀	♂	♀	Total	Per 1000 births	Per 1000 live births	Birthweight < 2500 g
Incidence of malformations of the C.N.S. at birth	6	1	18	23	48	1 10	0 96	13
Hydrocephalus, all cases	5	0	14	15	34	0.78	0 6[illegible]	8
Simple hydrocephalus	4	0	4	4	1	0 28	0 19	2
Hydrocephalus + *spina bifida cystica*	1	0	10	11	22	0.50	0 49	4
Spina bifida cystica all cases	2	1	13	18	34	0. 8	1.	9
Anencephalus, microcephalus, microhemisphere	1	1	1	1	4	0 1	0 1	2

Including one case with anencephalus.

hydrocephalics to avoid losing undiagnosed or unregistered cases. This was often so for cases with *spina bifida cystica*.

Study B The field study was made in 1961 and concerned a population of 650 000–660,000 inhabitants with 64,630 registered live births during the actual period, which comprised 6 years. The total number of live born children has changed from 10,480 to 11 060 per year during this time The study concerned all liveborn hydrocephalic children born in 1952–57 which were found in three different Swedish counties (Norrbotten, Uppsala and Örebro) up to the time of the study Questionnaires were sent to 186 district nurses, 24 nurses for mother and child care, 23 institutions for feeble minded, and 199 parish offices (where all causes of death in Sweden are registered) Answers were obtained from all. In this way information was obtained about all known or suspected cases, which were still alive as well as probably all dead cases with simple hydrocephalus, but probably only some of the cases with *spina bifida cystica* the dominant sign. The diagnoses of most of the cases were furthermore controlled from clinical records in the Departments of Pediatrics of Boden, Gallivare Uppsala and Örebro. All children still living except two, were reexamined by the authors and the diagnoses were confirmed. The two exceptions concerned operated children, where neurosurgical records verified an expansive hydrocephalus Among the dead children, 4 5 had been cared for in pediatric department and had been diagnosed there post mortems verifying the diagnosis were made in about half of the children. For the few remaining cases convincing clinical data was presented. The figures for the total number of live births and of all dead children in the district were obtained from the parish offices. The number of inhabitants in the different counties are taken from Statistical Abstract of Sweden 1954–1959 [19].

Results

Study A The incidence of all malformations in the central nervous system at birth was found to be 1 10 per 1000 births and 0 96 per 1000 live births, the figure for all live births being 42,779 during the period concerned The frequency figures for hydrocephalus and *spina bifida cystica* at birth are found in Table 1 The most reliable figure is the one for hydrocephalus with *spina bifida cystica*. It was found to be 0 49 per 1000 live births. The corre-

TABLE 2 *Incidence of infantile hydrocephalus apparent before one year of age in three Swedish counties (Study B)*

County	Uppsala	Örebro	Norrbotten	Total
Total live births during 1952 1957	15,253	21,022	28,355	64,630
Hydrocephalus, per 1000 live births	0.98	1.05	1.24	1 11
"Simple" hydrocephalus per 1000 live births	0.52	0.86	1 03	0.85
Hydrocephalus + *spina bifida cystica* per 1000 live births	0.46	0.19	0.21	0.26

sponding figure for simple hydrocephalus was 0 19 Among the 34 hydrocephalic infants of the 48 cases with malformations of the central nervous system 20 showed a clinical hydrocephalus at birth and 6 within the first few weeks of life In the remaining 8 cases the suspicions were confirmed at autopsy Hydrocephalus with *spina bifida cystica* (i.e myelomeningocele meningocele and/or encephalocele) occurred in 22 cases. Of the hydrocephalic children two had more than one malformation in the central nervous system One had hydrocephalus, aplasia of the corpus callosum and malformation of the base of the skull, the other had hydrocephalus and dysplasia of the right hemisphere. In the families of the whole group of 48 infants elder malformed siblings or siblings dying early in infancy had been born in 5 families (7 infants) Five of the 48 mothers had earlier had a total of 6 abortions. Of the 48 infants 22 were first children 5 were more than one month premature and 9 were at least 7 days postmature. The birth weight was less than 2500 g in 13 infants.

Study B The incidence of hydrocephalus with an onset before the end of the first year of life was found to be 1 11 per 1000 live births However incomplete information was obtained in Norrbotten and Örebro concerning dead cases with *spina bifida cystica* where not a few cases with unregistered hydrocephalus were probably hidden. Thus figures estimated to be reliable only applied to "simple hydrocephalus, the incidence of which was found to be 0 85 per 1000 live births in the combined three materials. The differences between the three counties are illustrated in Table 2

Among the 55 cases of "simple hydrocephalus 32 had died. In the group with *spina bifida cystica* only one child was still alive The relation of survivors to sex appears in Table 3 and was found to be 3 4 for boys and 1 4 for girls in the com-

TABLE 3 *Distribution of sex among 72 cases with infantile hydrocephalus in Study B*

	Dead 1961			Alive 1961			Total number
	♂	♀	total	♂	♀	total	
Hydrocephalus, all cases	24	24	48	18	6	24	72
"Simple" hydrocephalus	17	15	32	17	6	23	55
Hydrocephalus + *spina bifida cystica*	7	9	16	1	0	1	17

TABLE 4 *Comparison concerning the incidence at birth of infantile hydrocephalus (per 1000 total births) between earlier investigations and the authors study A*

	England Mackeown *et al.* [12]	Smithells [16]	U.S.A. MacMahon *et al.* [11]	Japan Neel [14]	Sweden South. reg. Böök [2]	Sweden Middle reg. Own material
Number of births	56,760	36,600	183,654	64,569	44,109	42,845
Hydrocephalus, all cases	1 76	1.6	1.85	1.22	0 90	0. 3
"Simple" hydrocephalus		0.3	0.90		0 84	0 25
Hydrocephalus + *Spina bifida cystica*		1.3	0.85		36	60
Spina bifida cystica, all cases	_.50	1.6	2.10	0 26	1 0	78

bined material. The number of deaths among all children born in the years 1952-57 within the three counties were 1505 up to the year 1961 Thus at least 3 3 % of the deaths concerned hydrocephalic children.

The incidence of malformations within the group seems to be high However exact figures cannot be given due to incomplete information concerning the dead children.

Discussion

When evaluating earlier reports concerning the incidence of infantile hydrocephalus, several factors make comparison difficult. These are differences in the definition and classification of infantile hydrocephalus, different ways of collecting cases, and a common lack of information concerning incidence figures in terms of a well defined population. Moreover large geographical variations undoubtedly exist perhaps best illustrated by a variation in the total frequency of cystical *spina bifida* from 0.26 per 1000 births in Japan [14] to 4.– in Ireland [4].

The incidence of infantile hydrocephalus has previously been studied usually together with the incidence of all sorts of congenital malformations present at birth [2, 3 4 9 12, 13 14 15]. Thus all cases of hydrocephalus independent of etiology have been included among malformations. As hydrocephalus has usually not been clinically exactly defined cases with non expansive hydrocephalus secondary to various sorts of atrophic brain lesions might well have been included. The figures in Table 4 where some representative investigations from different parts of the world together with ours are tabulated must be regarded with these reservation However this limitation does not apply to the very recent investigation by Smithells [16], the figures of whom exclusively relate to cases of expansive hydrocephalus recognised at birth in live and still-born babies of the Liverpool area.

Our material in study A is best comparable with the one of Böök *et al* [ ] from southern Sweden. Both are based on hospital cases from the same country but they are derived from different parts and periods. The material of Böök *et al* comprised 79 % of the total number of births within the district our material represents an average of 98 % (the last ten-yearperiod 99.5 %). Hydrocephalus has been differently defined in the two materials. Böök *et al.* used clinical routine case

history diagnoses, implying obvious sources of error according to our experiences from an earlier follow up study [6 7]. In our present material only cases have been included who showed an abnormally large growth of the skull confirmed as being an expansive hydrocephalus. The lower figures for "simple" hydrocephalus in our material are probably partly explained by these differences in the materials. However the differences might also partly be due to geographical factors. This presumption is further supported by the higher figures in Southern Sweden for all cases of *spina bifida cystica* a clinical diagnosis which leaves no doubt in interpretation. The larger proportion of hydrocephalic cases in our material of *spina bifida cystica* is surprising at first sight It is certainly explained by a number of revised diagnoses at reevaluation of clinical and post mortem data revealing additional cases with clinically overlooked but obvious hydrocephalus. The incidence figure for hydrocephalus in cases with *spina bifida cystica* found in our material in study A must be very close to the total incidence during the whole first year of life an assumption supported by data in study B

Reports concerning the incidence of hydrocephalus starting later in the first year of life are more scanty McKeown & Record [1_] in a prospective study from Birmingham found that the total incidence of hydrocephalus had increased from 1 76 to 2.57 per 1000 births between the ages of _ weeks and 5 years, i.e an increase of 0 81 per 1000 births. From Japan Neel [14] reported an incidence at birth of 0.22 per 1000 live births which had increased to 0 50 nine months later i e. an increase of 0.28 per 1000 Our experiences from this and earlier studies [6 7] reveal that the increase after the first few weeks of life probably only applies to "simple" hydrocephalus, as no new cases combined with cystic spina bifida had been added during the period when parts of study A and B overlapped. The figure for the increase in simple hydrocephalus derived from the two studies together was 0 66 per 1000 live births (0 19 to 0 85) Thus in only one of three to four infants with a condition of "simple" hydrocephalus was a diagnosis made during the newborn period.

The probable importance of geographical differences even within Sweden can also be traced from Study B where higher incidence figures for "simple" hydrocephalus were found for Norrbotten compared with Uppsala county This is especially noteworthy with regard to the better facilities for diagnosis in the easily accessible Uppsala county compared with the vast Norrbotten districts. However it cannot be concluded from these figures that the differences are not explained by chance But it should be quite reasonable to accept a higher incidence in Norrbotten county due to its isolated areas and special difficulties in communication favouring both prenatal and perinatal factors. The lower figures for hydrocephalus with *spina bifida cystica* in Norrbotten and Örebro compared with Uppsala are in all probability explained in another way They are certainly due to an incomplete registration of the hydrocephalic state when the main diagnosis was myelomeningocele This suspicion was confirmed from the Uppsala material, which was possible to follow up in detail.

In conclusion, it can be set down that

TABLE 5 *The calculated number of new cases with infantile hydrocephalus appearing per year in Sweden*

	Incidence per 1000 live births	Calculated total number in Sweden per year
Spina bifida cystica	0.49	49
Simple hydrocephalus	0.85	85
Total cases	1.34	134

the valid results from study A concerns the incidence of hydrocephalus with *spina bifida cystica* and from study B the average incidence of simple hydrocephalus starting before one year of age. In spite of obvious differences between the two materials they are both statistically representative and can be used together for an approximate calculation of the total yearly incidence of expansive hydrocephalus in Sweden. The incidence of hydrocephalus with *spina bifida cystica* was found to be 0.49 per 1000 live births in study A. The corresponding average figure for simple hydrocephalus was 0.85 in study B. This gives a total of 1.34 hydrocephali children per 1000 live births. As an arithmetical example this incidence figure can be applied to the present number of about 100 000 live born infants per year among the 7.5 million people of Sweden. This will give a yearly contribution of 134 new hydrocephalic children to the country (Table 5). The relevance of this frequency was controlled for simple hydrocephalus which has the largest clinical interest for surgical treatment. All new cases appearing in a region with a population of 1.3 million inhabitants (the Uppsala University Hospital region) were reported during one year 1961/62. According to our calculations 18 new cases ought to have been diagnosed, and 16 new cases were reported. Thus a satisfactorily good agreement was obtained.

7.5 mill. inhab., 100,000 live births per year

Summary

The incidence of infantile hydrocephalus in Sweden was investigated in two separate studies: the number of cases present at birth was determined in a material from an obstetric clinic, the number of cases with an onset during the first year of life was penetrated in a field study.

Among all 43,548 infants delivered at the Obstetric Department of the University Hospital of Uppsala in 1944–61 malformation of the central nervous system were revealed in 48 cases, i.e. 1.10 per 1000 births. The corresponding figure for hydrocephali births was 0.8. Hydrocephalus was combined with *spina bifida cystica* in 0.50 per 1000 births and in 0.49 per 1000 live births, while the corresponding figure for simple hydrocephalus was found to be 0.28 and 0.19 respectively.

In the field study made in 1961 and comprising all children born in 195–57 in three different Swedish counties a total number of 72 cases with infantile hydrocephalus starting before one year of age was found among 64 630 live births. Simple hydrocephalus was present in 55 cases, 0.85 per 1000 live births. Incomplete information was obtained in this study about the incidence of hydrocephalus in cases with *spina bifida cystica*.

The total incidence per year of new hydrocephali cases with an onset before one year of age was obtained by adding

the frequency figure for hydrocephalus with *spina bifida cystica* at birth to the frequency figure for "simple hydrocephalus starting during the first year of life. With this approximation a total incidence of 1.34 per 1000 live births was found i.e. 22 cases per 1 000 000 in habitants, or 14 cases of "simple hydrocephalus and 8 cases combined with *spina bifida cystica* The reliability of the frequency figures obtained was checked for "simple hydrocephalus from experience in practical clinical work during one year 1961/62, and a good agreement was found

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CASE REPORTS

Gastric Perforation in the Neonate

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Neonatal gastric perforation is an uncommon entity. A review of the literature has revealed only 100 cases. This entity was discussed as early as 1825 by Siebold [23], but the first attempt at a repair was not until 1929 [25]. This, however, was unsuccessful due to a reperforation. In 1950 Léger *et al.* [13] reported the first survival following surgical repair of a neonatal gastric perforation. Prior to that time all but one case had been discovered at post mortem [16]. In the last 1. years, there have been 60 recorded cases where surgery has been attempted. The results have been better with prompt intervention, but delay beyond 12 hours after the onset of symptoms has resulted in a sharp increase in mortality. This implies that immediate recognition and prompt surgery offer the best chance for survival. This report will present two cases of gastric perforation in premature neonates and again emphasize the necessity of prompt diagnosis and surgical intervention as the only means of increasing survival in this acute neonatal abdominal emergency.

Case Reports

Case 1

This 5-day-old girl was admitted on February 20, 1963 with history of recurrent attacks of cyanosis and progressive jaundice. The patient was born two months prematurely following an otherwise normal first pregnancy of a 19-year-old woman. The delivery was uncomplicated. The birth weight was 1590 g. Soon after birth the child began to have attacks of cyanosis and at the age of 3 days increasing jaundice. A chest film one day following delivery showed a small infiltration in the right lower lobe, probably due to aspiration. Physical examination on admission revealed slight jaundice and labored respirations but no other abnormalities. Several hours later the child suddenly became deeply cyanotic and markedly distended. Subcutaneous emphysema was noted in the left scapular region and the left flank. Breathing ceased and no heart sounds were audible. Resuscitation was started immediately and after half an hour the heart activity returned to normal. During the following hour, however, there were repeated episodes of cardiac arrest requiring closed heart massage for resuscitation. The patient was placed in an Engström respirator and blood and fluids were administered by a cut-down. Following these measures, her condition appeared to improve. Chest and abdominal films revealed a large pneumothorax on the right side and free intraperitoneal air (Fig. 1). Pleural suction drainage was instituted, following which the right lung fully expanded. With a preoperative diagnosis of pneumoperitoneum from a ruptured hollow viscus, an exploratory laparotomy was carried out on February 21, 1963. The abdomen was explored through a supraumbilical trans-



Fig 1 Case 1 There is large amount of free intraperitoneal gas and large right-sided *pneumothorax* *Note the subcutaneous emphysema along the left thoracic wall.*

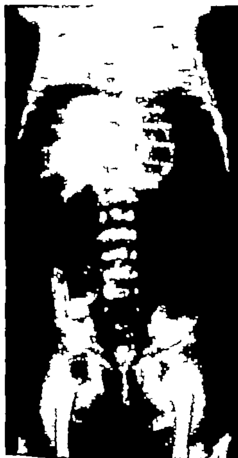
verse incision. The coils of intestine were edematous, discolored and matted together by a fibrinous exudate. A 1 cm perf ration with ragged edges was found along the lesser curvature near the cardia. The defect was losed with one layer of interrupted nylon sutures. The immediat postoperative course was complicated by repeated bout of cyanosis. The child became rapidly worse during the next few hours and died in apparent circulatory collapse Post mortem revealed extensive peritonitis, cerebral hemorrhage mediastinal emphysema, and multiple areas of bleeding in the limentary tract The stomach repair was intact.

Case 2

This 12-hour-old premature girl was born on February 25, 1963 after a normal pregnancy and uncomplicated delivery Her mother was a 31 year-old primipara said to have myoma of the uterus. The birth weight was 1340 g Due to prematurity the child was transferred immediately after birth to the Department of Pediatrics. Physical examination on dmission was normal except for mild cyanosis and obvious intercostal retractions. Th child was placed in an incubator and subsequently seemed t do well with normal color and spontaneous bowel movements. Three hours later however the abdomen became suddenly distended and she was deeply cyanotic. No peristalsis could be heard. A moderate degree of subcutaneous emphysema was present in the left and right flank A plain film of the abdomen revealed considerable free intraperitoneal air with marked elevation of the diaphragm (Fig. 2) With a preoperative diagnosis of neonatal gastric perforation, an exploratory laparotomy was carried out. The abdomen wa entered through a left paramedian incision. When the peritoneum was opened, air which seemed to be under increased pressure escaped. There was no free fluid or peritonitis present A 3 cm perforation was found in the anterior wall of the stomach nea the mid portion of the greater curvature. The edges of the perforation were sharp while the surrounding stomach wall was quit edematous and friable The perforation was closed in two layers with interrupted cat-gut stitches in the first layer and interrupted silk stitches in the second layer An omental patch was used to cover the suture line. The postoperative course was uneventful. On the 3rd postoperative day gavage feedings were started, which the child tolerated very well. These were discontinued three weeks later when she was started on oral administration of breast milk. The infant gradually increased her body weight and was discharged on April 21 1963 in an excellent condition.

Comment

In spite of numerous attempts to explain neonatal gastric perforation, the cause of this entity has not been definitely





b.

Fig. 2 (a and b). Case 2. There is massive free intraperitoneal gas with marked elevation of the diaphragm. Note the scrotal and lower abdominal subcutaneous emphysema.

proved. It seems possible however that several causative factors are involved. Among these, congenital defects of the gastric musculature is considered by many authors as the most significant [1 3 4 10 22]. In 1960 while reviewing the literature, Amadeo *et al.* found 14 cases of neonatal gastric rupture that were microscopically proven to have been caused by a congenital defect in the gastric musculature. To these they added three cases of their own bringing the total reported cases to 17. The fact that no biopsy was obtained from those cases that were successfully operated upon suggests that this anomaly may actually occur more often.

Overdistension of the stomach caused by a distal gastrointestinal obstruction has been reported as a cause of spontaneous perforation [5 9 24]. Gastric overdistension by a mechanical respirator used shortly after birth was thought to be the cause in the case reported by Purcell [20].

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SUMMARY OF SUPPLEMENTS

Papers Dedicated to Sture Siwe at His Retirement from the Professorship of Paediatrics at the University of Lund June 30, 1963

by A. WALLGREN and G. ENGLESON (Editors)

(Supplement 146)

Girl Swimmers With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects

by P O ÅSTRAND L. ENGSTRÖM, B O ERIKSSON P KARLBERG I NYLANDER, B SALTIN and C. THORÉN

(*Supplement 147*)

Thirty girl swimmers, aged 12–16 years, representing the top swimmers in four different clubs, were investigated with special reference to respiratory and circulatory adaptation and gynaecological and psychiatric aspects. Due to the difference between the clubs with respect to recruitment of swimmers for special training and to training conditions, the material was heterogenous It consisted of girls who were in the beginning of their training The evaluation of the physical and mental health and development, as well as of the social and family background revealed special features in the material. Most of the girls came from families belonging to the upper social groups. Most of their parents had formerly been active athletes and were extremely interested in the girls sports prowess, which they greatly stimulated and facilitated in various ways. The girls had an advanced growth expressed as an increased height in relation to age and a somewhat early menarch. They also had good or superior intelligence and were extroverted and energetic Both the history and medical examination showed that the series consisted of strikingly healthy girls. The gynaecological examination disclosed no signs of menstrual disturbances. In view of the presence of pathogenic organisms in the vagina in 12 of the 30 girls the risk of infection in connection with the swimming during menstruation was pointed out. The physiological studies showed that the girl swimmers taken as a group had an advanced functional development. The functional dimensions measured, i.e. lung volumes, total amount of haemoglobin, blood volume and heart volume as well as the functional capacity determined during maximal oxygen uptake were significantly increased in relation to body size There were, however considerable individual variations. The largest deviation was noted for the heart volume which, in some cases, was higher than the highest value hitherto

reported in bicycle ergometer tests in women. The functional development was related to the training volume The possible influence of constitutional physical training during a phase of rapid growth was discussed. The physiological studies during swimming showed that swimming at competitive speed requires maximal, or nearly maximal involvement of both aerobic and anaerobic energy producing processes. This was also supported by the good correlation between the top results achieved in competitions, expressed in points according to an international scale and the maximal oxygen uptake during the bicycle ergometer test. The investigation showed that these young girls hard swimming training can be regarded as a biological experiment Although it has hitherto exhibited no detrimental effects, it should be kept under careful control from the paediatric point of view Moreover the future development of the girls in the present series should be followed up In addition, a retrospective study was made of post-active female swimmers by means of a detailed questionnaire The results gave no grounds for suspecting that the swimming training would have any future detrimental effects either physical or mental, on the girls in the present series. On the other hand, the two groups are not fully comparable because of the less intense training in former years

The Physical Working Capacity of Healthy Children Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin D Supply

by HANS BERVEN

(*Supplement 148*)

Two groups of children, each consisting of about 30 children aged 10–11 years, were investigated with regard to physical working capacity (PWC_{170}) and its annual variations. One of these groups, the test group received vitamin D on two occasions on the one hand a daily dose of 1500 I.U administered continuously for a period of two months; and on the other single massive dose of 400 000 I U The effect of vitamin D on PWC which had previously been reported by several authors could not be shown to be of statistical significance The other group the control group, like the test group was subject to seasonal variations in PWC, with a significant minimum in late autumn Nov.–Dec. and a maximum in April–May The causes of the observed seasonal variations have been discussed, and it seems that, to a great extent they were due to variations in physical activity on account of differences in climate and in the length of daylight during the

year In a smaller group the effect was studied of UV irradiation on PWC heart volume blood volume and total haemoglobin in comparison with those of a control group No effect of UV irradiation which was of statistical significance was observed in connection with the test group With regard to PWC and heart volume both groups showed similar seasonal variations as those found in the larger material. In connection with blood volume and total haemoglobin, a somewhat divergent course was noted, as they increased during the entire period of investigation. The increase was however slightly larger during the spring months in comparison with that which was observed during the period Oct.–Dec and consequently it appears that also these parameters were subject to some seasonal variations.

Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion

by TIMOS VALAES

(*Supplement 149*)

The effect on bilirubin of exchange transfusion (ET) performed in the presence of marked hyperbilirubinemia is presented. Seventy three such ET performed in 63 infants are analyzed. In 28 infants the severe jaundice was attributed to liver immaturity while the remaining were cases of hemolytic disease of the newborn In 34 ETs the procedure was interrupted in the middle for approximately 30 minutes (two-stage ET) In all cases measurements of hemoglobin, hematocrit and serum bilirubin were carried out on samples collected at the beginning and at the end of the procedure and at the beginning and at the end of the rest period in the two-stage ET Samples were also collected 30 min after the ET in 14 cases. Moreover the same measurements were carried out in the blood removed during 36 ET The volume exchanged was on the average 2 4 times the estimated blood volume (estimation based on 85 ml/kg body weight) and the average rate of ET was 33 minutes for the exchange of each unit of blood volume. By comparing the changes on intravascular mass of bilirubin on the one hand and the amount of bilirubin removed on the other hand it was concluded that during the ET a shift of bilirubin from the tissues into the vascular compartment occurs and thus the serum bilirubin concentration is sustained at a level higher than expected while in all our cases the amount of bilirubin removed exceeded the initial I–V mass of bilirubin. The shift of bilirubin from the tissues into the blood stream continues for a while after the ET and evidence is presented that on the average equilibrium between the two

compartments is reached within 30 min The drop in serum bilirubin concentration produced by ET was found to be variable Expressed as percentage of the initial serum bilirubin value it ranged from 38 % to 73 % with an average of 55 %. The rate of exchange and hematocrit changes did not influence the drop in serum bilirubin concentration. When the ET produced an expansion of the plasma volume this led to increased shift of bilirubin from the tissues into the plasma and thus the effect of dilution of serum bilirubin was counterbalanced. The amount of bilirubin removed from the tissues expressed as percentage of the initial I–V bilirubin was again variable ranging from 40 % to 180 %. It was larger in the two-stage ET and in those where a decrease in hematocrit occurred. The amount of bilirubin removed from the body expressed as percentage of the initial I–V mass of bilirubin was on the average 130 % in the one-stage and 150 % in the two-stage ETs. The amount removed was not influenced by the rate of exchange but a linear relationship existed with the size of exchange when the latter was measured by the ratio plasma removed initial plasma volume An equation was developed which made possible the estimation of the total readily available bilirubin (extracellular bilirubin) from the results of the ET and the rebound of serum bilirubin following it The readily available bilirubin was found to be 3 to 4 times the I–V bilirubin and 1/3 to ½ of this was removed by the ET It was concluded on the basis of the findings of the present investigation that the most favorable conditions for the fulfilment of the purposes of ET in cases of hyperbilirubinemia are secured by an exchange of 200 ml/kg b w using fresh heparinized blood of an hematocrit of 40 % and a technique that minimized mechanical damage of the transfused cells.

Iron Requirements in Infancy

by PETER JOHAN MOE

(Supplement 150)

Iron-deficiency anemia still occurs in a large percentage of infants aged 6 to 24 months in spite of being an easily preventable disorder

The earlier recommendations in the literature for daily iron allowances were based mainly on studies using balance technique in a small series of infants. Most recommendations in the more recent literature are based on calculations of the iron needed by hypothetical infants during various periods up to the age of 1 to 2 years These calculations can serve only as a rough guide The most reliable recommendations for the daily iron allowances in infancy were presented by STURGEON in 1958 STURGEON carried out his studies on a large number of infants receiving various amounts of medicinal iron without any close dietary supervision.

There are so far no reliable data in the literature on the iron requirements in infancy based on studies with food iron.

The present study was performed on 237 healthy infants, from a well baby clinic, receiving various amounts of food iron during the first year of life The infants were followed up monthly there was constant dietary supervision, and blood test were performed every third month All the infants received iron fortified cereals from the age of 3½ months. Groups A, B and C were selected at random at the age of 3 months. Group A consisted of 67 infants groups B and C of 85 infants each (to allow for subgrouping) The iron content per 100 g cereal for the three groups was.

Group A. 20 *mg* (19–24.8) + Fer In-Sol
15 mg
Group B 12,5 *mg* (9.2–12.5)
Group C: 5 *mg* (2.3–5)

In addition, 33 infants outside the main study were included for comparison at the age of 12 months They had received either no iron fortified cereals or iron fortified cereals with a low iron content (group D)

Total daily iron intake in the different groups of infants is shown in a table

It has been demonstrated in these studies that a large proportion of the infants receiving significantly less than 10 mg iron daily from the age of 8 months (groups C and D) will develop iron-deficiency anemia during the first year of life This iron-deficiency anemia is easily preventable. A dietary iron intake of approximately 10 mg from the age of about 8 months (group B) will produce normal hemoglobin concentration in almost all infants with a maximum mean hemoglobin concentration of 11 60 g per 100 ml at the age of 1* months The final proof for the existence of a preventable type of iron-deficiency anemia is the excellent response of the anemic infants to iron therapy

The infants were divided into subgroups based on detailed dietary studies of each infant. *The subgroups receiving 10 1–12* mg iron/day (and the subgroup receiving 0.9–0.99 mg iron/kg body weight at 12 months of age/day) from the age of 8 months achieved a ceiling for hemoglobin concentration at 12 months of age

Factors other than iron intake influencing the blood values of infants are briefly discussed. There seem to be good reasons for presuming that breastfed infants have *about the same iron requirements as artificially fed infants.*

It is concluded that this investigation shows that a daily dietary iron intake of about 10 mg (or 0.9 mg/kg wt at 12 months/day) from the age of 8 to 12 months will produce optimal hemoglobin concentration in almost all normal infants. The iron requirements during the first 4 months *of* life are minute, then gradually increase *to the above stated level*

From a practical point of view it is important to know that an iron content of 12.5 mg per 100 g of iron fortified cereal, when cereals are fed regularly twice a day from the age of 3½ months, will assure adequate iron supply for the normal infant

Preventive Paediatrics in the Undergraduate Curriculum Symposium Held with the Collaboration of the World Health Organization at the X International Congress of Paediatrics Lisbon 1962

by B. VAHLQUIST (Editor)

(Supplement 151)

I Introductory lectures

E. Grzegorzewski. Prevention in the undergraduate medical curriculum

R. Debré The concept of preventive paediatrics

D B Jelliffe and F J Bennett Different problems in different parts of the world

M Graffar Scope and place of preventive paediatrics in the undergraduate curriculum

Read, J H Methods of teaching preventive paediatrics. Physical aspects

J Richmond Methods of teaching preventive paediatrics Mental aspect

II Round table. the situation in different areas of the world

1 Chile J Sommelet Vicuña
2 Colombia J D Wray
3 Czechoslovakia J Houstek
4 Italy E. Schwarz Tiene
5 The Netherlands: G M. H. Veeneklaas
6 Senegal. J Senecal
7 Sweden B Vahlquist
8 Turkey J Dogramaci

Acta Pædiatrica 52: 608–632, Nov 1963

PROCEEDINGS OF PEDIATRIC SOCIETIES

The Danish Paediatric Society

Meeting Sept 20 1961

Henning Andersen An Infant with Jadassohn-Lewandowsky's Syndrome

The patient was an infant with premature dentition, changes in the finger and toenails resembling onychogryposis, coarse features with thickened skin and a tendency to hyperhidrosis.

S Vestermark Acut Suppurative Otitis Media in Children under Two Years of Age

Published in *Ugeskr Laeg 123* 1415, 1961

J H Probst Continued Experience with Decadurabolin in Children with Muscular Dystrophy

DISCUSSION

Th Lauresen In the Central Laboratory Rigshospitalet Copenhagen, we have in collaboration with Dr Probst, compared the serum lactic acid dehydrogenase and the serum aldolase in cases of progressive muscular dystrophy Determination of serum aldolase is time-consuming and unreliable and investigation revealed that it can be replaced by determination of lactic acid dehydrogenase. The reason for the raised serum enzyme level may be changes in the walls of the muscle cells in progressive muscular dystrophy or increased production of enzymes in the muscle tissue It is noteworthy that Durabolin therapy causes an increase in the serum enzyme levels. Further enzyme electrophoresis of lactic acid dehydrogenase was undertaken. By this method, lactic acid dehydrogenase is split into three fractions differing from the fractions which come from the heart and liver It is noteworthy that, in an isolated case, during treatment with Durabolin, occurrence of an extra enzyme fraction was demonstrated. These investigations will be continued. — *N P Friis* Reported a girl aged six years who had suffered for the past three years from rapidly progressive muscular dystrophy She was treated with the anticholinesterase alkaloid, Nivalin, in daily injections of increasing strength for 60 days. The improvement thus achieved has remained unchanged for two months since the cessation of treatment.

Meeting Oct 11 1961

N Tygstrup Demonstration of a Child with Jaundice of Unknown Origin

J Melchior Oligodendrocytoma in a Boy Suffering from Recklinghausen's Disease

The patient was a boy aged 12 years with Recklinghausen's neurofibromatosis with definit fibromata and café-au-lait patches. In addition, his mental development had proved to be subnormal. At the age of four years, his I.Q. was found to be 89 He was re-examined the subsequent year in the same place and the I Q was then 81 At that stage the pneumo-encephalogram showed increased quantities of air frontally During

subsequent years, the boy was in a residential nursery and, shortly prior t dmission t Rigshospitalet he was submitted to in estigation in a Department for Child Psychiatry where the EEG was found to be slightly abnormal and calcifications were demonstrated over the sella turcica. Repeated pneumo-encephalography confirmed the suspicion of a tumour Suprasellar exploration revealed the right optic nerve to be twice as thick as the left and little tumour Microscopic examination from this rendered the probable diagnosis of oligodendrocytoma. The case history illustrated the occurrence of intracranial conditions in Recklinghausen neurofibromatosis. A in this case these most frequently consist of oligodendrocytomata. Some obscure points in the in estigation and the intervention could possibly be plained if the boy had another tumour poss bly a pinealoma, but he w not f llowed-up sufficiently long for this to be determined.

I K udsen Neurosurgical Treatm nt of Hydrocephalus

DISCUSSION

B Friis-Hansen drew attention t an article by O'Neill in *Arch D Ch ld 36* 41 1961 From the cranial measurement in several hundred hildren examined from birth throughout a prolonged period growth curves have been constructed which with great certainty permit decision whether given head will develop hydrocephal s. — *P Plum* drew ttention t J stesen curves of cranial growth n Danish infants.

Meeting Nov 8 1961

Bent Friis-Hansen Osteochondritis of the Head of the Humerus

A case of osteochondritis of the head of the right humerus is reported in a child aged five years. When the child was two and half years of age the mother had lain on the hild right arm one night. The arm was tender for some days thereafter A year later transient pain in the arm occurred The child was brought because there was slight muscular atrophy in the right upper limb and insignificant limitation of external rot tion of the right shoulder joint Radiography revealed a translucent area in the medial epiphysis of the head of the right humerus of 4×6 mm. The condition wa quite unchanged on control examination two months lat There were no serological changes and radi graphy of the remainder of the keleton showed normal conditions.

C. Fridericksen. Acut Interstitial Myocarditis in Infancy as the Cause f Sudden Death

On the basis of the clinical picture in breast fed baby of eight months with sudden symptoms of cardiac failure and with demonstrable enlargement of the heart a review is given of the clinical observations mad in recent years concerning interstitial myocarditis. Two main groups are concerned.) myocarditis of unknown etiology and b) caused by the Coxsackie virus B 2, 3, 4 5. Th disease may occur both sporadically and epidemically Coxsackie infection may manifest itself in four different w ys: 1) the herpangimous form, type A 1–6, 2) the myalgic form, type B 1–3–5, 3) aseptic meningitis, type B, type A 1 9 and 4) the myocarditic form type B 2–3–4–5. The first three forms are benign and the fourth more serious the younger the patie t affected It may be the cause of sudden death. The first cases were reported from South Africa in newly born infant from various maternity nits while an epidemic of Bornholm disease was present in the population (Sylvest disease – epidemic myalgia) In the infant affected, the same Coxsackie types B 3 and 4 were found as in the patient with myalgia. In Europe m ocarditis was first described by van Creveld and de Jager in 1936 during an epidemic of summer influenza In addi

tion to the perinatal cases, the disease may be transferred to the foetus in utero, should the mother suffer from epidemic myalgia aseptic meningitis shortly before delivery In addition to affection of the heart the brain, liver pancreas and suprarenal glands are also involved. Type B is always in volved and this is found in the faeces, cerebrospinal fluid or post mortem, in frozen (−*0°C) tissue from the heart. It is possible that the Coxsackie virus also plays a part in derma tomyositis in children. In this country the Coxsackie virus occurs both as types A nd B. The possibility of an epidemic of Born holm disease must be envisaged. Doctors assisting t deliveries and paediatricians should be aware of the interstitial myocardi tis which may follow epidemic myalgia and aseptic meningitis.

DISCUSSION

I Boesen mentioned two cases of infants with cardiac failure from Queen Louise s Hospital for Children. One infant suffered from fibroelastosis and the other from a suspected trio- ventricular communication and both had raised GO-transaminase le- vels. It is thus doubtful whether determina tion of GO-transaminase is of any conclusive alue in the diagnosis of acut myocarditis infants. Percutaneous myoendocardial biopsy was mentioned (*Ame Heart J 60* no. 3) This investigation was undertaken without complications in one patient in Queen Louise s Hospital and the diagnosis of fibroelastosis verified — *Ol f Andersen* thanked Dr Friderschsen for the very sti mulating and inspiring lecture He considered that a not inconsiderabl number of cases of acute myocarditis due to the Coxsackie virus in infants are diagnosed and die in the guise of pneumonia. The disease may also occur in older hildren. Reported a case in a girl aged three years in Queen Louise Hospital. The clinical picture resembled, in many ways, that described by Dr Friderich sen but virus culture was not vailable in 1952. — *P Perregaard* reported a case from The Paediatric Department in Blegdams- hospitalet in which a boy aged 14 months died after an acute stormy illness lasting only for a few hours. Autopsy revealed pronounced myocarditis, bronchopneumonia and acute meningo-encephalitis. The simul taneous occurrence of meningo-encephalitis and myocarditis makes infection with the Coxsackie virus probable — *Henning Frede riksen* mentioned investigations fo Cox sackie virus in the State Serum Institute If practitioners find type determination of the Coxsackie virus to be of particular signi ficance they are requested to make arrange- ment with the Serum Institute concerning these very expensive and very time-con suming investigations. It is noteworthy that even broad spectrum antibiotics have no effect upon this type of virus but that the newly-discovered virus-inhibiting sub- stance Interferon, will perhaps prove to be of significance in Coxsackie infections in infants.

Niels Tolstrup Hereditary Galactosaemia. Enzyme Measurements in View of Diagno- sis and Mod of Inheritance

The subject was introduced by mention of the symptoms occurring during a milk diet treatment with milk-free diet and its signi ficance for the survival and normal develop- ment of the patients. Thereafter the results of measurements of the erythrocyte concen- tration of the enzyme, galactose-1 phosphate- uridyl transferase in 108 individuals by a quantitative method established by the uthor were presented. Thirty eight of these individuals constituted a control group who did not belong to families with galactose- mia and 65 were relatives of the five cases of galactosaemia (five families) From the enzyme concentration, the material may be subdivided without overlapping int three groups: normal (genotype AA) with normal enzyme concentration, conductors (genotype Aa) with reduced enzyme con centration and patient (genotype aa) with enzyme concentration 0 The pedigrees show that the disease is inherited recessively The

division figures for the distribution of the genotypes in siblings are compatible with recessive heredity The biochemical-genetic and pathogenical features of the disease which belongs to the group of inborn errors of metabolism, are mentioned. Thereafter the practical significance for the diagnosis of the enzyme measurements was stressed. It is emphasized that the diagnosis then becomes independent of the manifest in jurious symptoms so that the milk free diet, so important for the prognosis, may be in stituted immediately following clinical suspicion. It is stressed that by demonstration of the aetiological factor viz. the enzyme defect, specific diagnosis is established. The significance of this in the otherwise difficult differential diagnosis from galactosaemia due to other causes is illustrated with examples (familial diffuse interstitial fibrosis of the liver and de Toni Fanconi's syndrome). Centralization of the analyses is facilitated by the fact that the method est blished by the uthor does not require any special treatment of the samples of blood prior t transport. An xample is quoted to illu strat how quantitativ enzyme measurement may be employed as a hereditary prog nostic aid. Finally it may be mentioned that the incidence of this rare disease ma be cal culated by determination of the much greater incidence of conductors in the nor mal population.

DISCUSSION

P Plum. Does the disease exist in various degrees f severity in the population? — *Tolstrup* The disease is only known t occur in one degree of severity — *J Oster* Has galactose tolerance been attempted in the heterozygotes? — *Tolstrup.* I have not ttempted such investigations but others have The results were inconclusive on ac count of the influence of other factors. — *B Friis Hansen* mentioned galactosuria due to other causes.

Meeting Dec. 8 1961

Annual meeting with ladies. Ide Leppenthin M.A. spoke and showed slides on "The Child in Art"

Meeting Jan. 10 1962

K. Wilken Jensen: Allergy to Cow Milk

Some children in the age group 4–12 years show series of different symptoms from the skin, nose ears, blood and alimen tary canal all of which are caused by allergy t milk and milk products which can be demonstrated by limination diets and provocation tests. Among the examples there were patients both with and without familial predisposition, eosinophilia and cutaneous reactions

Published in *Ugeskr Laeg 124* 1049 1962.

A. Frøland and B. Zachau-Christiansen. Two Infants with 45 Chromosomes

An enlarged version of this paper was published with the title *Ovarian Dysgenesis (Turner Syndrome) in the Newborn, Acta Path Microbiol Scand, 57* 21 1963.

J Schultz Larsen Indications fo Chromosome Investigations in Clinical Practice

Extraordinary Meeting Jan 15 196

J A. Andersen (Department of Paedia trics, University f Minnesota) Ammonia Metabolism in Hepatic Disorders.

Members of the Danish Medical Society and the Danish Society for Clinical Chemistry and Clinical Physiology were invited to this meeting.

Meetmg Febr 14 196*

P Pl m. Demonstration of Apparatus for Intelligence Testing of Physically Handi capped Children

H Hamtoft and P Plum. Variations in the Incidence of Prematurity in Recent Years

This paper will be published later

DISCUSSION

A L. Willumsen mentioned investigations undertaken by himself and others which sug gest that the incidence of prematurity is significantly greater in mothers who are heavy cigarette smokers, particularly in th latter part of pregnancy than in mothers who do not smoke.

Grethe Holst Dental Surgeon Points of Common Interest Between P ediatrics and Odontology

Members of the Danish Odontological *Society were invited to this meeting*

E. Thamdrup A Girl with Constitutional Premature Puberty Treated with 17 ethinyl-19-nortestosterone

The patient was a girl with constitutional premature puberty with development of the breasts from the age of 10 months. The first menstruation occurred when she was 14 months of age From the age of four years she was treated with 17-ethinyl-19-nortestosterone (Norlutin® Parke Davis & Co) in *daily oral doses of 10 mg for two periods of* one year with an interval of two and a half months. During treatment, distinct reduction in the size of the breasts was observed and the menstrual periods diminished in degree and number The excretion of oestrogenic hormone and gonadotrophic hypophyseal hormone which were increased prior to treatment remained unaltered. On the other hand, the oestrogenization of the vaginal epithelial cells disappeared almost entirely Prior to treatment, the growth in height and development of the bones were considerably accelerated. During treatment the acceleration of bon development was reduced while the growth in height remained unchanged. The treatment did not result in any signs of virilization. The investigations undertaken do not suggest that 17-ethinyl 19-nortestosterone in the dosage employed had any gonadotrophin-inhibiting effect but that it did inhibit the influence of oestrogen on the tissues. The inhibition of bone development demonstrated must be presumed to imply a greater final height for the patient as the time of closure of the piphyses is postponed

Meeting March 14 1962

H Dyggve J Melchior and J Clausen M rquio-Ullrich Syndrome. Abnormal Ex cretion of Acid Mucopolysaccharides

DISCUSSION

N *Hobolth* Dorffmann albumin precipi tation technique is adequat for the demonstration of acid mucopolysaccharides in the urine for ordinary clinical use Employing this technique patients with familial cart laginous exostoses and arachnodactyly nd the relatives of these patient were examined In addition, patient suffering from gar goylism, Morquio-Silverskiöld disease foetal chondrodysplasia hypertrophic familial osteoarthropathy (two patients), Waardenburg' syndrome and idiopathic hypercal caemia (Fanconi-Schlesinger type) were investigated. The excretion of acid mucopolysaccharides was found to be increased only in patients with gargoylism. The investigation did not confirm the supposition that cartilaginous exostoses and arachnodactyly are mucopolysaccharide anomalies.

Sv Brandt and J Mertens Operation on the Hamstring Muscles in Spastics. (Patient demonstration)

This paper will be published elsewhere

Sv B ndt A Brief Review of Mechanisms to Increase Tone

H E. Jørgensen Excretion of 3-methoxy-4-hydroxy mandelic-acid (MHMA) in Sympathetic Tumours

E. Rysting Hypophosphatasia

A review is given of the manifestations, prognosis and therapy of the disease. The case of a girl aged two years without known predisposition to bone disease was mentioned. In this case the typical clinical picture of the benign form of hypophosphatasia which develops rather late was encountered. About the age of one year she lost four incisor teeth but did not present any other symptoms until she was referred on account of pain in the right leg and accentuation of right genu valgum. The diagnosis was verified by demonstration of phosphoethanolamine in the urine and reduction of alkaline phosphatase activity in the serum, leucocytes and skin biopsy and the characteristic radiographic irregular ossification in the metaphyses of several of the long bones. Both of the parents have normal alkaline phosphatase activity in the serum and do not excrete phosphoethanolamine in the urine

Published in *Ugeskr Laeg 124* 1797 1962

Meeting May 9 1962

Folke T dred The Congenital Nephrotic Syndrome

The patient was a girl aged thirteen months in whom the nephrotic syndrome was demonstrated at the age of one month. She was born one month prematurely and the birth weight was 2,400 g Steroid therapy had no effect on the proteinuria and the blood chemistry Percutaneous renal biopsy undertaken at the age of 11 months showed slight mainly proliferative, changes and a considerable degree of focal glomerulitis while the tubuli were normal. The prognosis is poor The majority of cases of the nephrotic syndrome demonstrated within the first year of life die before the age of two years.

B Zachau Christiansen and Torben Iversen The Respiratory Distress Syndrome in Newly Born Infants. Preliminary Experience in the Treatment of Acidosis

The clinical findings and the pathogenic factors in the respiratory distress syndrome (RDS) are reviewed and, in particular disturbances in the acid base metabolism (respiratory + metabolic acidosis) and the possible significance of a patent ductus and of low serum protein are mentioned Usher' treatment of the acidosis with sodium bicarbonate in 10% glucose solution is mentioned. During the period Jan. 1961–April 1962, 25 infants with RDS were admitted to the Children s Hospital, F glebakken, Copenhagen. Of these, 14 were treated conservatively (incubator oxygen and antibiotics) and 11 of these died The remaining 11 infants were treated with 10% glucose-bicarbonate via the umbilicus. Eight of these died but four of these must be considered to have been insufficiently treated (too late in the course of the disease or too little bicarbonat) In infants with RDS, the following average values were found during the first 24 hours of life: pH 7 16, pCO 49 mm Hg and standard bicarbonate 15 mEq/l, while values in non-dyspnoeic premature infant were: 7.37 33 mm Hg and 19 mEq/l, respectively In the management of this condition in f ture attempts will be made to ensure earlier institution of treatment and increased initial administration of sodium

bicarbonat By means of serum protein determinations, normalization of any low values encountered will be ttempted.

DISCUSSION

B Friis-Hansen mentioned an investiga tion involving premature infants in the weight-group 1 000–1,500 g from Maternity Department A, Rigshospitalet Copenhagen. The investigation was conducted in co-operation with the Central Laboratory The serum lectrolytes, pH pCO_2, oxygen satura tion, serum proteins and blood sugar were investigated. The object of the investigation was t lucidat the spontaneous course in these infants and to compare the values in the infants who survived with those in the infants who died as it was not considered that Usher investigations concerning these conditions were sufficiently comprehensive and, in particular it was not st ted how long prior t death the high serum potassium values were found. The preliminary result is that the serum potassium was high, but not strikingly higher in the premature in fants in whom death occurred part from isolated agonal values. The most striking finding, on the other hand, was that the pH was very low and the pCO high and perhaps the most pronounced feature was the nega tive base-excess and low oxygen satura tion in the infants who died. Administration of too much fluid to these infants was not recommended as the anoxia must be inter preted as the central factor in the clinical picture and the respiratory acidosis can scarcely be improved by administration of bicarbonat — *Poul Kildeberg* Acidosis in newly born infants may be due t many factors. In premature infant with respira tory distress, a low pH may have many causes. Apart from the combined acidosis, purely respiratory and purely metabolic acidosis may be encountered. The latter may for example occur on account of a transient disproportion between acid pro duction and renal acid limination or as remnant following combined acidosis when oxygen administration is est blished. I con sider that the respiratory condition depends entirely upo he form of acidosis concerned. The severe c nued (uncompensa ed) forms of acidosis pre t the most serious therapeu tic problems nd in these cases bicarbonat treatment by t he method is sociated with considerabl heoretical disadvantages. A patient with base-excess of 15 mEq l and pCO_2 of 59 mm Hg may have pH of bout 7 10 In such patient pproximately 7 mEq l of the existin buffer base def cit will be distributed in the non olatile buffer systems of the blood. If the pH be nor malized by administration of b ar nat treatment must continue until E CO (157 ml) are released per litre bl d If a patient can maintain a constant pCO during the period of treatment approximatel 1 mEq l blood would bring the pH up 35 as increase of the bicarbonat concentration will constitut approximat ly 14 mEq l. If the patient retains, however 70 of the CO released, the bicarbonate metabolism will increase t approximat ly 50 mEq l blood and, at the conclusion of the treatment, the pCO will have increased to pproxi mat ly 100 mm Hg (In these reviews, the difference between the bicarbonat concen tration in the blood and the plasma has not been taken int consideration.) A low pH may prove fatal but carbon dioxide narcosis may also be lethal. Thus, administration of very great quantities of bicarbonat con cerned and thus involves a risk of overloading these patients with fluid, sodium ions and CO all of which are unfavourable in the presence of respiratory distress. The risk is greatest in the patient who require treat ment most. It may be added that in the Paediatric Department in Odense we have on several occasions, observed combined acidosis with even very low pH values (bout 7 00) disappear as soon as ventilation and administration of oxygen were established. I believe that prophylactic measures such as infusion of albumin and attempts to supply as much oxygen as possible have more to offer therapeutically Possibly the so-called "tris buffer" (THAM) will prove to be of significance particularly in the treatment of combined acidosis. — *N Hebolik* On the

basis of the discussion which has arisen concerning the significance of the serum proteins for the development of respiratory distress, reference is mad to Domville Cooke s work and the preliminary results of treatment with infusions of serum albumin in the Paediatric Department, Copenhagen County Hospital in Gentofte are mentioned: During the period of investigation the serum proteins in capillary or cord blood were measured in the premature patients. Total proteins of less than 5% were found in 16 patients and to all of these 1 g human albumin was administered intravenously. During this period, five premature infants died two from cerebral haemorrhage one with cerebral haemorrhage + atelectasis and one with atelectasis and hyaline membrane No autopsy was undertaken in the fifth patient but the infant did not present signs f respiratory distress. The results hitherto obtained are very promising and encourage con inued trial. — *Sten Møllerts.* These patients have a combined metaboli and respiratory acidosis. The metabolic acidosis i slight and, as an isolated phenomenon it would be without significance but in these cases, however it accentuates the low pH. It can, to a certain extent, be lleviated by bicarbonate On the other hand, when the patient receives sufficient oxygen the surplus of organic acids will be oxidized t bicarbonate and the final result may be a metabolic alkalosis if bicarbonate has been administered to a certain extent. On the other hand, very little can be achieved by treating respiratory acidosis with bicarbonate Expansion of the extracellular fluid phase will merely occur with a tendency t oedema. What is wrong is that the patient cannot breathe and causal treatment is artificial respiration. As far as I am aware, there are considerable practical difficulties in such treatment in any case when hyaline membranes have formed as ften traumatic emphysema is obtained in the patent section of the lung without the other sections of the lung being ventilated. Haglund in Gothenburg Sweden, has worked with respirator therapy in newly born infants. I do not consider that much can be achieved by treatment with THAM (or "tris") An adult excretes 20 to 30 mol carbonic acid per 24 hours while renal excretion amounts to 0 1 mol acid and the total renal excretion is of the order of a few mol per 4 hours. The substance is not atoxic. I consider that attempts should be made to elucidate the aetiology and pathogenesis of the disease and that particular interest should be paid to the extracellular volume, the plasma volume and the sodium concentration (i.e. the osmotic conditions) the humidity of the inspired air and oxygen saturation (the oxygen supply of the organism). I would like to point out that a low oxygen saturation may exist together with a normal pCO where there are difficulties in diffusion and defective ventilation of sections of the lungs with retained circulation. — *Zachau-Christiansen and Iversen* in reply t *Friis-Hansen.* We have undertaken potassium and sodium determinations in healthy premature infants and patients suffering from RDS Potassium levels appear to be highest in the latter but determinations on both capillary and venous blood have proved unreliable on account of haemolysis. The sodium values are perhaps slightly higher in infants suffering from RDS To *K ldeberg* We were also hesitant bout the massive administration of bi carbonate but as Usher s results were so promising and the prognosis of the condi tion without treatment so poor w conside red that attempts at treatment were permissible. We have not attempted treatment with "tris" which is said to be rather ir ritating locally To *Hoboth* The attempt at treatment with administration of albu min seem to be promising W have com menced investigations of the serum protein in infants with RDS and in their mothers, but have not yet obtained a sufficiently ex tensive material.

E. Thamdrup Electrolytes in the Sweat in Children with Recurrent Pulmonary Infections

The object of this investigation was t investigat the incidence of mucoviscidosis

among Danish children with chronic or recurrent non-tuberculous pulmonary conditions. The content in the sweat of sodium and potassium were examined by the method elaborated by Grønbæk (Grønbæk, Paller: Studier over natrium og kalium udskilt i sved. København, 1959). The material comprised 38 children (20 girls and 18 boys) aged from 3 months to 13 years. Of these patients, three had bronchiectasis, two lung abscesses, two cystic lungs, one bronchial adenoma and the remainder recurrent bronchitis or pneumonia. One of the patients had suffered from severe dyspepsia during the first and second years of life five patients suffered from very slight dyspepsia and the remainder had never had dyspeptic symptoms. Excretion of sodium and potassium were normal in 36 patients, doubtfully abnormal in a boy aged ten years with chronic bronchitis and definitely abnormal in a girl of 12 years with severe bronchiectasis. In the boy the sodium excretion in the sweat was 114 mEq/l and later 69 mEq/l and the ratio between sodium and potassium 2.9 and 2.8. He had not suffered from dyspepsia. In the girl aged 12 years, the sodium excretion was found to be 146 mEq/l and later 118 mEq/l and the ratio between sodium and potassium was 4.7 and 4.2. She had never experienced dyspeptic symptoms and the content of trypsin, amylase and lipase in the duodenal juice was normal. The investigation confirms the observation that there are patients with chronic pulmonary conditions without dyspepsia but with changes in the sweat similar to those in mucoviscidosis. The cases in this material are not so frequent as in a number of German and British works which have been published in recent years. The divergences are perhaps due to different methods of collection of the sweat and various interpretations of the normal values of the composition of sweat.

DISCUSSION

P. Grønbæk and J. Vesterdal Larsen. As a preliminary supplement to Dr Thamdrup's material, the results of determination of the sodium/potassium ratio in the sweat in adult patients with pulmonary conditions and gastric ulceration from Medical Wards F and B, Frederiksborg County Hospital, Hillerød, are presented. The result are immediately comparable with Thamdrup's result as both the technique and the normal materials are common. The advantages of testing the sodium/potassium ratio in the sweat rather than individual values of sodium and potassium are emphasized. The material comprised 39 patients, 15 females and 24 males aged from 15 to 75 years. Of these patients, 23 had chronic bronchitis, three bronchiectasis, eight gastric ulceration and, finally five had chronic bronchitis and gastric ulceration simultaneously. These latter patients were regarded in advance as being particularly suspect for mucoviscidosis. All of the patients showed a normal sodium/potassium ratio in the sweat. This result is surprising when compared with previous communications in the literature. As a preliminary impression, the rarity of mucoviscidosis, including here classical fibrosis of the pancreas in Denmark is emphasized. — *H. Andersen.* Did not recommend the placing of too much emphasis on the sweat test alone in the diagnosis of fibrosis of the pancreas. The value of the more difficult and time-consuming investigations of the enzymatic content of the duodenal juice was emphasized.

S. Vestermark. A Case of Vasopressin-Resistent Diabetes Insipidus

A case of vasopressin-resistent diabetes insipidus occurring in a boy is reported. At the age of two years, a fall in diuresis of 61% with the Carter Robbins test occurred but in 1961 increasing dehydration occurred with prolonged limitation of fluid supply. Intravenous urography showed a dilated ureter on the right side. Selective renal investigation showed reduced ability to concentrate on both sides. Explorative laparo-

tomy did not reveal any stricture nor obstruction of the ureter Both the mother and a sister had reduced specific gravity of the urine after thirsting for 12 hours.

DISCUSSION

J Vesterdal asked if the capacity to render the urine acid was reduced in these patients. — *S Vestermark* did not think it was.

Meeting May 11 1962

Meeting in common with The Scandinavian Society for Research on Mental Subnormality

Professor H Bickel, (Marburg): Phenylketonuria

E. Wamberg Incidence of Phenylketonuria in N tional Institutions for Mentally Subnormal

K. Vellmand Two cases of Phenylketonuria treated with Zymogran

A H Arnfred Report of A Girl Aged Thirteen Years with Treated Phenylketonuria

A Dupont R. Guthrie s Method f Investigation f Phenylketonuria

The proceedings of the meeting are reported in the minutes of the Society for Research on Mental Subnormality

Meeting June 12 1962

Members of The Obstetric and Gynaecological Society and the Danish Anaesthetists Society were guests at this meeting

Professor J A Miller and Dr Faith S Miller Tulane University New Orleans, U.S.A.: Lecture and film dem nstration: "Hypothermia, a New Approach to Asphyxia of the Newborn"

O Secher demonstrated a Danish ppara tus for hypothermia in newly born infants.

Meeting Oct. 3 1962

P Agner Rasmussen and B Zachau Christiansen Reticulosarcomatosis in Twins.

Published in *Acta Pædiat (Stockh), 52* 522, 1963.

Folke Tudred and S Guldberg Tuberculin Reaction in School Children who were Calmett V ccinated in the Neonatal Period

Out of 1,220 newly born infants vaccinated in 1950 (see *Da ish Med Bull, 3* 122, 1956) 1 014 were traced in schools. Of these 13 were or had been tuberculin negative (1.28%) The remainder 1 001 were tuberculin positive 7–10 years after vaccination. Out f 11 children who were found to be tuberculin negative bout the age of two months, seven were traced at school and all of these were positive although only two of them had been re-vaccinated.

An animated discussion took place in which the members of the Danish Tuberculosis Society who were guest at the meeting participated. The discussion concerned the correct time for Calmett vaccination et Opinions varied greatly and nother meeting between tuberculosis physicians and paediatricians was agreed upon.

P Plum Thalidomid Embryopathy

Demonstration of a case and mention of various prenatal lesions. This paper was published in *Ugeskr Laeg* *124* 1227 1962.

H Andersen [illegible]monstrated, in t[illegible] ormec tion, a child [illegible]th 17–18 trisom[illegible] nd con genital deform[illegible]es

H[illegible] ng Andersen C[illegible]p[illegible]hage

Meeting Oct 10 1962

J B. Fawcett (Manchester) Neonatal Pulmonary Radiology with Special Reference t Premature Infants

John Lind (Stockholm) Neonatal Respiration

Meeting Nov 14 1962

J Flamand Christensen. Demonstration of Bodice-Harness with Webbing Bands for Attachment t the Mattress

C. Hansted. Method of Obtaining Blood Samples in Infants

By employment of Vacutainer Tubes (glass t bes with vacuum to which [illegible]xalat [illegible]trat heparin etc. had been added if required for special purposes) in connection with the Vacutainer Plastic Holder equipped with an adapter with Luer connection (Becton, Dickenson & Company Rutherford, N J U.S.A) together with the Scalp Vein Infusion Set (Abbott) withdrawing of samples of blood is greatly facilitated. In infants, samples of blood from 5–10 ml may be obtained in this way from cranial veins and several samples can be obtained from the same venepuncture by changing the Vacutainer tube The taking of blood samples is facilitated somewhat if the catheter is filled in advance with a solution of heparin and it may be of advantage when cranial veins are concerned, to rotat the oblique cut surface of the cannula away from the skin so that the tendency of the vein t collapse is reduced.

N Hebsikh. Hereditary Nephropathy (Alport s Syndrome)

Hereditary nephropathy (H.N) is being diagnosed with increasing frequency The symptoms are haematuria and possibly proteinuria which are accentuated b[illegible] ercurrent diseases and pregnancy In males it leads to uraemia and early dea h The syndrome is frequently accompanied b inner ear deafness. Two affected families are mentioned.

In the first family the disease w[illegible] encountered in three or possibly four generations. Among the 22 descendants of [illegible]w man who had possibly H.N., a total of eight (three females and five males) were found to suffer from H.N Two of the males had died from uraemia. There were no definit cases of reduced hearing or diseases of the eye in this family The mode of inheritance is typical sexlinked dominant. The second family includes three generations. Among 24 descendants of a woman with nephropathy and reduced hearing ten individuals (four females and six males) were found t have H.N alone while one female had H.N and reduced hearing and another female had reduced hearing and a renal calculus which, however can scarcely be [illegible]ttributed to H.N All of the adults and the majority of the [illegible]hildren in the first family were investigated for an antibody to renal tissue and by immune electrophoresis without positive results. The excretion [illegible]f protein in the urine suggests increase of glomerular permeability as in chronic glomerulonephritis with a nephrotic element. In the differential diagnosis, it is most important t exclude chronic glomerulonephritis. The diagnosis is based upon the clinical symptoms and demonstration of the hereditary factor

DISCUSSION

E Thamdrup In 1956, two sisters with glomerulonephritis were admitted to The Children's Hospital, Fuglebakken, Copenhagen. In these patients the disease was classified as hereditary nephritis. This condition, which is most frequently inherited from the mother appeared, in our patients, to originat from the father who died t the age of 32 years from chronic glomerulonephritis. In his case the disease was discovered by demonstration of haematuria on routine examination of the urine when he was admitted to hospital at the age of 6– years. After the death of the father the mother arranged to have the urines of her three children tested. There were two girls aged 9 and 8 years and a boy f 1 1/* years. The boy's urine was normal. The girls showed haematuria and proteinuria. They were kept in bed for six months without any effect upon the symptoms, as the urine persistently contained 10–30 (maximally 50–100) erythrocytes per field on microscopic examination and there was constant slight proteinuria. The renal function blood pressure urography and cystoscopy showed normal findings. There was no pyuria and no bacterial growth was obtained on culture (including culture for tubercle bacilli) There were no .s of haemorrhagic diathesis. There was reduction of hearing In both of the patients, the tonsils were enlarged with signs of chronic infection. The antistreptolysin titre and the antistreptococcal hyaluronidase inhibitor were slightly raised for a period and, for this reason, tonsillectomy was undertaken. After a period of bservation of five years, the conditions in these patients and, in particular the urinary findings were stationary

H Rørsing S Brünner and H L G Wulff Kerosene Poisoning in Children with Special Reference to the Radiographic Changes

Cases of kerosene poisoning in hildren occur frequently although practically always with only a few slight symptoms. As an introduction, the symptomatology and conditions of resorption of the poison are discussed. During the period 1949–1961 92 children suffering from poisoning with hydrocarbons, the majority of which were cases of kerosene and turpentine poisoning were admitted to the Department of Paediatrics in the Gentofte County Hospital. Sixty per cent of the cases were in boys and poisoning ppeared to occur almost exclusively in the age group 1–3 years. In only one case were there severe clinical symptoms. In the great majority of cases, the amount of poison taken was unknown. Radiographic investigation was undertaken in 46 out of the 92 patients and positive findings were present in 40 children. Two types of radiographic changes occur the first consisting of small cloudy infiltrates with a tendency to confluence (aspiration type) and the second of granular perihilar infiltrates (oedematous type) Fifty four of the 92 children were examined clinically and radiologically In on case slight pulmonary tuberculosis was found but the other 53 did not present any clinical symptoms. Radiographic investigation revealed slight changes in 12 of the patients.

DISCUSSION

O Steinicke. During the period Jan. 1 1958–Nov 1 1962, the following cases of poisoning in children were admitted to the Department of Paediatrics, Sundby Hospital, Copenhagen: 19 cases of kerosene 11 of turpentine 6 of petrol and 3 cases of furniture polish poisoning Of these 39 cases, 26 were boys and 13 girls. Thirty six of the children were between the ages of 1 and 2 1/* years, two were three years of age and one child was six years old. Clinically the children were surprisingly little upset by the poisoning Only 11 presented acute symptoms on admission and these symptoms consisted mainly of weakness and lethargy One child was, however in extremely poor condition on admission and was practically moribund with cyanosis and failing respiration. All f the children were submitted to radiography of the lungs and this investigation was undertaken in 34 of the cases from

4 to 36 hours after admission. Out of the 38 children examined, slight to moderate dif fuse consolidation was found basally in the lungs and, in the majority of cases mainly corresponding to the right lung. On control radiography 6–14 days after the first in vestigation, the pulmonary changes had disappeared in 12 out of the 14 children mentioned and, in the remaining two child ren, the hanges disappeared in the course of some weeks. — *C Frederiksen* The fall in temperature following sulpha or penicillin therapy in kerosene pneumonia occurs distinctly later than in the bacillary forms. In 1931, I reported case of turpentine pneu monia to this Society and emphasized the two different forms: aspiration pneumonia, resembling the lipoid pneumonia described by Brastrup following administration of Rimidol nasal drops and resorption pneu monia in kerosene poisoning. Animal ex periments on rabbits have shown that pneumonia may occur as early as one hour after injection of kerosene intraperitoneally. As the gastro-intestinal barrier thus appears to have been surmounted very rapidly gastric lavage must be undertaken almost immediately after ingestion of the poison and in cases where a more prolonged interval has elapsed, the parents should be warned of the possibility of subsequent pneumonia or the child should be admitted for observa tion. In many of the cases reported in the literature, recurrence of the pneumonia took place and, in our case this occurred shortly after discharge t the home. The X-ray photographs shown by the lecturer illu strat very beautifully the two different forms of pneumonia.

C. J Sievers A Case of Megaloblastic Anaemia

A case of megaloblastic anaemia with si multaneous occurrence of proteinuria and free gastric acid is reported. The case resem bles the ten cases described by Imerslund in *Acta Paediat* in 1960 and a similar case was described by Gräsbeck & al. in *Acta Med Scand* in 19 The disease en ty has not been descri elsewhere in th omewhat scanty litera re on megaloblastic naemia in children. Th child in questio was three years old at h commencement of the disease She wa dmitted with high pyrexia which had been preceded by fatigue for a couple of months On admission, she was found t have pneumo nia and a Hb of 33 %. Smears of blood and bo marrow revealed megaloblastic naemia Th patient was treated immediately with transfu n of blood and dministration f vi n B_{12} aft which a marked increase in he reti culocyt count was observed. In h course of 1 1/2 months, a total of 300 mic ograms vitamin B_{12} was administered plus mg in connection with two Schilling test There- after she was followed an out pa ien t without any vitamin B_{12} therapy and after nine months the serum B_{12} was found to be pathologically low During the entire illness proteinuria was present The bsolut quan- tities were not great but the electrophoretic picture was markedly pathological and sug gestive of the clinical picture of the neph rotic syndrome. Free gastric acid was pre- sent the pH being 4 Schilling's test revealed defective absorption of B_{12} by the standard test and after administration of the intrinsic factor prior to the test The intrinsi factor and the gastric juice of this patient had the same effect when administered to patient with known pernicious anaemia prior to the Schilling test. This proves that the child has an intrinsic factor and thu does not suffer from pernicious anaemia. Finally megalo- blastic anaemia on account of leucaemia, haemolytic anaemia, inadequat diet ali mentary conditions, pancreatic f brosis, coeliac disease, diseases of the liver parasitic conditions, myxoedema and hypoparathy roidism was excluded.

DISCUSSION

O H *asted* It is the modern conception that d xylose is bsorbed in the proximal section of the small intestine and vitamin B_{12} in the distal section of the small intes- tine A normal result of the d xylose test

does not therefore exclude malabsorption and the pathologically low Schilling test + the presence of the intrinsic factor suggest that a condition of malabsorption does, in fact, exist. Regional ileitis is suggested as a possible cause of this.

Ruth Schjødt-Pedersen: A Case of Congenital Suprarenal Hyperplasia with Salt Loss

A female infant aged six days was transferred to the Gentofte County Hospital in September 1961 on account of failure to thrive. The birth weight was *050 g and the weight on admission was 1900 g. On admission, the infant was thin and looked premature. She fed reluctantly and vomited frequently. At the age of 1* days, increasing pigmentation and growth of the labia majora and the clitoris were observed. During the subsequent days the condition deteriorated further, the infant being greyish and hollow-eyed with reduced turgor and gasping respiration. Treatment with intravenous saline, percorten and hydrocortisone had an immediate dramatic effect. During the first days of therapy the degree of hydration was somewhat variable and parenteral glucose saline was required. Treatment continued with percorten intramuscularly and supplementary sodium chloride orally. After a few days, the condition was satisfactory and the child began to thrive. She was discharged at the age of two months. Prior to discharge an implant of 100 mg percorten was inserted and treatment with cortisone and sodium chloride continued at home. The patient was brought to out-patient control, was well and thrived normally. The total 17-ketosteroids varied somewhat between 1 and 2 (prior to treatment ...4) mg/24 hours. At the age of ten months, the patient was readmitted on account of pyrexia, vomiting and haematuria which subsided in the course of a few days. She was readmitted again at the age of 12 months after a catarrhal infection showing signs of incipient crisis. Parenteral fluids and extra cortisone and percorten were required. During this treatment, the child recovered and after a new implant of percorten she could be discharged in good health but microscopic haematuria of unknown origin still persisted. The problems in this patient were: establishment of the diagnosis and administration of a suitable dosage of cortisone to normalize the total excretion of 17-ketosteroids without inhibiting growth and the appropriate times for any re-implantation of percorten and, finally, the haematuria.

DISCUSSION

O. Hansted: Urography might have revealed a renal malformation. — *B. Friis-Hansen*: As mentioned previously it was believed that the suprarenals in these patients formed an abnormal hormone which directly caused the salt loss. More recent investigations have not confirmed this theory and, in this connection, I can report that, in Queen Louise's Hospital for Children, we have had two children with the adrenogenital syndrome and salt loss. In order to investigate how they reacted t stress, massive doses of ACTH were administered under close clinical observation and with simultaneous investigation of the sodium and the fluid balance. Clinically no changes were observed and the fluid and electrolyte balance did not alter either during treatment with ACTH and, in particular, no increase of the sodium excretion occurred. This thus suggest that these children do not react differently from other children with suprarenal insufficiency and it therefore suffices to ensure that they receive sufficient cortisone, percorten and sodium chloride and to emphasize that the dosage must be increased should acute episodes occur. — *E. Thamdrup*: In children with congenital hyperplasia of the suprarenal cortex and disturbances in electrolyte regulation, very dangerous states not infrequently arise in connection with infections particularly during the first two years of life. As vaccinations may result in pyrexia, it is advisable to postpone the prophylactic vaccinations until after the age of two years unless, on account of epidemiolo-

pical conditions, the danger of infection is considerable. If pyrexia occurs, the usual dose of cortisone should be doubled

Anna Sørensen A Case of Hypoglycaemia with Convulsions n Account f Inadequat Production of Adrenaline

The patient was a boy aged scarcely three years. The birth weight was 500 g and development had been normal or perhaps slightly retarded. The child was admitted on account of repeated episodes of unconsciousness and convulsions which occurred bet ween 9.30 a.m. and 1.30 p.m. with simul taneous hypoglycaemia (blood sugar 30–42 mg%) The EEG was moderat ly bnormal on admission and normal 14 days and two months later The most important causes of spontaneou hypoglycaemia are severe dise se of the live hypofunction of the an terior lobe of the hypophysis, adrenocortical hypo'unction, sever myxoedema, lesions of the central nervous system particularly in the region of the hypothalamus, pronounced renal glucosuria and organic hyperinsulinism. A 4 hour fasting test was undertaken and revealed fall in blood sugar t below 50 mg % during the first 15 hours (according to Wilkins, this excludes organic hyperinsuli nism). Further investigation revealed that the so-called idiopathic spontaneous hypoglycaemia in children was concerned (McQuarrie 1954). In this group, two further causes of spontaneous hypoglycaemia have been lucidated, viz sensitivity t leucine and disturbances in adrenaline production. The former can be excluded by oral and n travenous tolerance tests In leucine sensi tivity a fall in blood suga t below 50 of the original value is observed 20–40 minutes fter intravenous administration of leucine Treatment of leucine sensitivity consists of low-protein diet possibly combined with low doses steroids. The ord could possibly be placed by ephedr ne Finally investigati n in view of poss bl distur bances in adr naline product on the pe riods of hypogl caemia were ndertaken (insulin loading fractionated in estimations of adrenaline nd be excretion of noradrena line in the urine before and after the ad ministration of insulin) The n merical result and the linical findings suggest re duced production of adrenalin with hypoglycaemia as the explanation of the attacks in this patient. The boy w r eat d with ephedrine every morning and noon and kept well thereafter It is important t tablish the diagnosis as the convulsions use ir reparable damage

DISCUSSION

P W Brestrup considered that the insulin test was not without danger but t is mport ant to establish the diagnosis. *J Oster* It is important that the diagnosis is established early Had observed numerous unrecognized cases in institutions for mentally subnormal

Anne Nygaard Emptying f the St mach with Ipecacuanha

In order t illustrat the value of ipeca cuanha as an agent to cause emptying of the stomach instead of gastric aspiration, 153 hildren aged from 4 months t 8 1 2 years received concentrated ipecacuanha in doses of 15 ml to children under one year and 20 ml t children over one year If vomiting did not occur in the course of 10–20 minutes, the same dose was repeated. One hundred and nineteen hildren, i.e nearly 78 % reacted effectively t the treatme t None of the children were particularly influenced by the poisoning but a few had slight symptoms.

Meeting Dec 8 196*

Combined meeting with The Danish Orthopaedic Society The Danish Neurological Society and The Danish Physiurgic Society in Copenhagen

W J W Sherrard Immediat Operative ertion Del yed Closure of Myel meningocele

(Published in *Arch Dis Child* 35 18, 1963)

R. B. Zachary (Sheffield): Management of Hydrocephalus by Spitz Holter Valve

W. J. W. Sherrard: Orthopaedic Problems (Paralytic Deformities) in Myelomeningocele

R. B. Zachary: Bladder Problems in Myelomeningocele

Meeting Dec. 13 1962

Jens Bjerre: "Stone Age People in the Atom Age"

Lecture and film about the primitive natives in the central Australian desert.

Meeting Febr. 13 1963

Ingrid Thern: Galactosaemia

An atypical case of galactosaemia is reported. A boy aged nine months was admitted on account of hepatomegaly and hydrocephalus. There was no known predisposition to similar conditions in the family. The increased circumference of the head had been observed from the age of two months but there had been no other symptoms until the age of five months. Since then, alternating pyrexia of unknown origin, irritability and failure to thrive had been observed. At the age of seven months hepatomegaly and the distinctly hydrocephalic shape of the head were apparent. The general condition was poor and the development retarded. On admission, reduced liver function was demonstrated and liver biopsy showed cirrhosis with steatosis. Pronounced aminoaciduria was present and intermittent proteinuria. There was bilateral cataract and the EEG was slightly abnormal. Pneumoencephalography showed communicating hydrocephalus with a considerably dilated ventricular system. The blood sugar was normal. No sugar had ever been demonstrated in the urine. After exclusion of other conditions, absence of uridyl transferase activity in the blood which is diagnostic for hereditary galactosaemia was demonstrated. Prompt improvement of the clinical condition and the abnormal laboratory findings resulted after withdrawal of milk and milk product from the diet. The increased growth of the circumference of the head ceased. The metabolism of galactose and the clinical findings and the history of galactosaemia are reviewed. The recent possibilities of treatment with orotic acid will be described in detail by Hermann. In this case, the presence of hydrocephalus and absence of galactosuria were atypical. In future patients with hydrocephalus of unknown origin will be investigated in view of galactosaemia.

L. Sparre Herman: Treatment of Galactosemia

In autumn 1962 a communication was published from Japan concerning the favourable effect of orotic acid in galactosemia. A dosage of 1 g daily was administered for two weeks to two patients (aged seven months and four years) after which distinct improvement in the clinical condition occurred. If erythrocytes from one of the patients were incubated under anaerobic conditions with galactose etc., addition of orotic acid (or uridin) resulted in normalization of various abnormal metabolic conditions. Orotic acid is a precursor of the nucleic acids. It is possibly a vitamin for certain animals and is present in cow's milk. Its favourable effect in galactosemia is possibly due to increased metabolism of galactose-1-phosphate. In patients with galactosemia, the metabolism of this substance is blocked as the patients have reduced uridyl transferase activity. In adults,

galactose-1-phosphate may be metabolised in another manner viz. with the aid of UTP (uridin triphosphat) In infants, who have a great UTP requirement for the synthesis of nucleic acid etc this must be done via uridyl transferase It may now be conceived that orotic acid, by increasing the UTP concen tration shunts" galactose-1 phosphat past uridyl transferase Several communications are available in the literature concerning the clinical employment of orotic acid. In parti cular it is said to have a favourable effect upon the liver disturbances. No side-effects have been observed to result from its clinical employment. If it comprises 1% of the diet, rats develop a slight reversible fatty liver which can be counteracted by adenin. In Germany a preparation which contains orotic acid, adenin and other purines (Pu rinor) has been introduced. It can be concei ved that this preparation may be of great significance in the treatment of galactosae-mia as it can prove difficult to maintain a rigidly milk free diet

DISCUSSION

Ole Mortensen. Test papers are now avail able to demonstrat galactose in the urine. — *P Plum* Investigations concerning the f fect of orotic acid on jaundice in non-sensitized premature infants is very desir ble

P Kildeberg· M tabolic Alkalosis in Congenital Hypertrophic Pyloric Stenosis

The results were presented of an investiga tion into the physiological aspect of the metabolic alkalosis accompanying hypertrophic pyloric stenosis in infancy On the basis of material comprising 185 determinations of the acid base st tus in 70 consecutive cases of pyloric stenosis (Astrup micro equipment) and supplementary mea surements of the net acid excretion and urine and serum electrolyt values, the fol lowing conclusions were reached: 1) Meta bolic alkalosis of moderat and severe deg rees is a common occurrence in hypertrophic pyloric stenosis with vomiting of a few weeks standi g 2) The alkalosis is due to continued gastric losses of H frequently in connection with failure of the renal compen sation possibl due to sodium and potassium depletion and increased adrenal cortical activity 3) The alkalosis runs a distinctly bi phasic course in patients undergoing surgical treatment The postoperat ve rise in base excess is probably related t in creased release of aldosterone but may be due to several factors. 4) Respiratory com pensation in alkalotic infants with pyloric st nosis is significant and effective Through out the scale of metabolic disturbance re spiratory compensation limit the change in pH to pproximately one half of the cor responding change in "metabolic pH (pH t a constant and normal pCO_2).

DISCUSSION

O Fredericksen E. Kirk was the first t describe alkalosis in congenital hypertrophic pyloric stenosis

J Worm M thaemoglobinaemia Due t Poisoning of Water in a Well

In the Paediatric Department in Randers and Odense two cases of methaemoglobin aemia were observed in autumn 1962 in infant of three and six weeks of age who had received mixed milk feeds made with water from defectiv wells which were situa ted a few yards from middens, latrines, drains and manured turnip fields The water from the wells was bacteriologically unsatisfactory The nitrat content was 390 and 495 mg (NO_3) litre and the nitrit con tent 0.57 and 0 10 mg (NO_2) litre It is con cluded that in Denmark water is occa sionally employed for infant feed which has such a great nitrate content that under un fortunate circumstances dangerous met haemoglobinaemia may result Greater control by the Health Authorities ppears t be necessary (Published in *Ugeskr Laeg* 125 797 1963).

DISCUSSION

\ *Hobolth*. In connection with the men on of acquired methaemoglobinaemia, it hould be noted that methaemoglobinaemia nay occur a a hereditary disease. In the rganism, a constant oxygenation of the valent ferrous atom of haemoglobin to the rivalent ferric atom with resultant forma on of methaemoglobin occurs. As the result a redox hain, the last link of which is the nzyme diaphorase the methaemoglobin is unmediately reduced to haemoglobin Im mediately after birth, the diaphorase activity is reduced and this may have been a contributary factor to the fact that only the infant in the family mentioned by Worm developed methaemoglobinaemia. Absence of diaphorase may occur as an inherited defect Such patients are permanently cyanotic and may possibly be diagnosed as suffering from congenital heart disease There is a considerable infantile mortality on account of inactivation of haemoglobin. Treatment is prolonged administration of ascorbic acid.

Meeting April 17 1963

Combined meeting with The Danish Society for Research on Rheumatism and The Danish Physiurgic Society in Copenhagen

M Getz and O Remtig Rheumatoid Arthritis in Children

Pall Eggert Joh nsen and B Friis Hansen: The Significance of Laboratory Findings in Rheumatoid Arthritis in Children

The result of various laboratory in vestigations in relation to rheumatoid arthri tis re reviewed on a material of 34 children collected during the period 1950–1961 in Queen Louise Hospital for Children Copenhagen. For comparison, the same problems are mentioned in 14 children suffering from acute rheumatic fever three children with a monoarticular joint affection and four hildren with transient" joint symptoms with durations of from one to four weeks. Seven of the hildren with rheuma toid arthritis had normal ESRs (micro method) during the entire course of the disease On f llow-up examination under taken from one to ten years after the com mencement of the disease 24 of the patients with heumatoid arthritis had normal ESRs and, of these ten were healthy ten slightly affected and four moderat ly affected. Six patient had ESRs of between 16 and 30 mm/hour and of these one was health and five moderat ly affected. Finally three patients had ESRs between 31 and 60 mm/hour and all of these were moderately af fected. Otherwise, a greatly raised ESR during the course of the disease appears to be a poor prognostic sign but, conversely normal ESR does not exclude the possibility that the patient may end in the poorest group. On follow up investigation, the RA test was definitely positive in two patient with heumatoid arthritis. One of these had been healthy for four years while the other a girl of 17 years, was crippled by the disease The Waaler Rose reaction was negative in all of the patients with rheumatoid arthritis on follow up examination. On investigation for antinuclear antibody with the anti human-globulin consumption test with hog pancreas nuclei as the antigen on follow-up examination of the rheumatoid arthritis patients, a definitely positive reaction was found in three out of 11 healthy patient (27%) in five out of ten sl ght cases (50%) and in seven out of 12 moderately ffected cases (60%). From this it may be conceived that in cases where the condition ha become quiescent clinically some connective tissue inflammation is still present I the 34 patient with heumatoid arthritis, 24 were girls and ten boys. On follow-up examination only four of the girls were

healthy while eight of the boys were healthy I a relatively much greater percentage cure in boys than in girls in the material available

Ib Frimodt Lindbjerg: Rheumatoid Arthritis in Children. A Material from The Department of Paediatrics, Rigshospitalet, Copenhagen

The material comprises 75 children suffering from chronic rheumatoid arthritis admitted to The Department of Paediatrics, Rigshospitalet during the years 1944–1962. The distributions according to age and sex and the clinical findings t the commencement of the disease correspond t those in other extensive materials. The patients were followed up in 1962. In 2" patients, no sequelae of the disease could be demonstrated in 26 there were minor changes, 17 patients were seriously crippled by the disease and five patients had died. The condition on follow-up examination was poorest in the patients in whom the disease commenced with pronounced general reaction in the form of raised ESR, pyrexia, leucocytosis and anaemia. Positive serum reactions were only present in a few cases. N relationship could be demonstrated between a positive serum reaction and the prognosis. In 31 patients, the gastric secretion was investigated by the Diagnex test on f llow-up examination and achlorhydria was revealed n four cases. No difference could be demonstrated in the prognosis for the material as a whole and for the group of patients (total of 46 here the dis commenced aft the introduct eroid therapy

Eleonor F b B rthe L d Else Marı I alear B ll g Rheumatoı ı arthritis in Children. A I mited Mater from Copenhagen

The material cons of hildr ith chronic rheumatoid art ı (p l agen Municipal Paediatric Deputm t l ıng the period 1949–1962 \ ˜ lren are invol ed, 14 girls and f ı red 1–13 years t the commencem he disease On follow up investıg l 14 years fter the commencement of the se the children were 4–19 years of age U first dmission, nine patient were ın S l and Stage II. Treatment varied in the o of years according t different principle physiurgic therapy salicylic acid preparations, gold salts, steroids, chloroquin derivatives and eradication of possible foci of infection. On follow-up examination, n children were found t be healthy seven were in Stage I, four in Stage II, one in Stage III and one in Stage IV Functionally 17 were in Class I and the two remaining cases in Class III. No conclusions can be drawn from such a limited material.

DISCUSSION

B Sury mentioned a follow up investigation of his previously published material ten years after the published results. The prognosis wa practically unchanged. — *P Plum* emphasized that the prognosis for the groups f severe cases was still poor

Meeting May 29 1963

Th. Rosendal Aplasia d Hypoplasia f the Labyrinth Foll wing Thalidomide

Malformation of the external ear and the external meatus are not unusually bserved as the only xternal lesion in thalidomid hildren. A an example of bilateral malformation of the xternal ear of the labyrinth and of the internal meatus, which have not previously been mentioned in the literature the following case is mentioned:

The father was aged 31 years and manic-depressive and the mother was a healthy primipara aged 24 years. During the period from the 4th to the 34th days after conception, the mother received 100, or t the

most 200 mg thalidomide A living female infant was born at term. Microtia was found on both sides and a peripheral facial paresis on the left side. The external meatuses were small and the tympanic membranes could not be discerned There were no reactions to acoustic or vestibular tests. The infant had, in addition an atrial septal defect and a ventricular septal defect with a left right shunt The extremities were normal. Radiographic examination of the temporal bones did not reveal any structures which could correspond to the semicircular canals or the cochlea which are normally fully developed at birth. In the left pars petrosa, at the site of the labyrinth an area of translucency as large as a pea surrounded by dense boney structure was demonstrated. This finding suggest arrest of development of the labyrinth at the otocystic stage Death occurred as the result of the cardia condition at the age of four months. Autopsy revealed that the internal auditory meatus and the coustic nerve were absent on both sides. In the heart atrial and ventricular septal defects were found. (The result of th histological investigation of the temporal bone will be reported later) This is thus a case of a thalidomide infant with bilateral microtia, aplasia of the labyrinth and of the acoustic nerve and of the internal meatus on both sides. Malformation f the inner ear has, hitherto been extremely rare and only a few reports are available concerning changes in th development of the labyrinth in experimental animals. Thalidomide infants should be investigated in view of malformations of the labyrinth as such malformations will have serious consequences during growth. Finally thalidomide should be investigated experimentally t produce hanges in the development of the labyrinth in experimental animals.

Ib Beesen: The Prognosis in Congenital Heart Disease in Infants and Toddlers

On the basis of the death certificates from 1938–1961 and presuming that four per thousand of all newly born infants have congenital heart disease, the chances of survival for these patients until the age of four years are calculated. Fifty per cent of the newly born patient survive the age of one year 47% survive the age of two years and 45% survive the age of four years. On account of the hyperbola-like curve for the times of death, from which it is apparent that the chances of survival increase relatively considerably if the infants survive the first 5–6 months, it is concluded that accounts of the prognosis in which infant are not subdivided into suitably small age groups render no useful information. Employing ventricular septal defect in infants as an example the prognostic significance of both the age at the time of investigation and of the systolic pressure in the right ventricle are illustrated.

DISCUSSION

E Sandoe Where infants with isolated ventricular defect are concerned, it is emphasized that the infants who survi e the first year of lif nearly always improve considerably during the second year of life. As a rule, improvement in the clinical condition is observed and, in a number of patients, the haemodynamic conditions undergo favourable alterations. In The Cardiological Laboratory Medical Department B, Rigshospitalet, Copenhagen, 74 patients with isolated ventricular septal defect have been examined The ages of the patients at examination varied between 2 and 50 years. As judged from the histories vailable 38 out of the 74 patient had been very ill during infancy Not only had they been 10–30% *underweight but they had* also suffered from repeated, prolonged pyrexial infections of the respiratory tract On investigation in The Cardiological Laboratory normal or nearly normal weight and height were found in all of the 38 patients who had failed to thrive in infancy Twenty nine out of the 38 patients were not inconvenienced or only slightly inconvenienced by their cardiac lesion whil the remaining nine patients were handicapped to an extent

TABLE 1 *Congenital cardiac diseases in infa Queen Lou se Children s Hospital 1955–1/5*

Radical or palliative operation perf d

		Age t op- n (months)					
		≤ 6		> 6 l		> 12 4	
	T tal	Liv	Died	Liv	D ed	Li	D ed
Pat. duct. art.	43	12		10	2		
Coarctation							
Without O A.	14	5		5			
With O.A.	8	1	5		2		
Valv aort. ST		1			1		
Aortic ring	8	6	1	1			
Transposition							
(Blalock Hanlon op.)	5	2	2	1			
Ventr sept. def							
Dammann-Muller op.	12	5	4		2		1
D. M. Albert	2-	15	5	6	1		
Fallot tetralogy							
Shunt-operation	26	7	2	6	1	1)	
Pulm. valvulotomy	1	1					
Total	151	55	21	29	11	24	1

corresponding to functional Group III Considerable pulmonary hypertension with an verage pressure in the pulmonary artery of over 50 mm Hg was found in 20 out of the 38 patients while 17 had normal or almost normal average pressure in the pulmonary artery (under 30 mm Hg).

Frederik Therkelsen The Possibilities of Operative Treatment in Congenital Heart Disease in Infants and Toddlers

In Queen Louise's Hospital for Children, Copenhagen, since 1955 195 children under two years were operated upon by closed methods which are also employed in lder patients. In addition, 26 children, of whom seven were aged less than two years, were submitted t open cardiotomy in a heart lung machine. These operations were carried out in Department R, Rigshospitalet; the children, after investigation in Queen Louise Hospital, being transferred t Rigshospitalet

I. *Operation by "closed" methods.* (See Table 1)

As will be observed from Table 1 the operation planned was successfull, performed in *151 cases* In 44 cases, it did not prove possible to carry out an adequat operative correction. In the majority of cases this was due to anatomical conditions (e.g short subclavian artery or hypoplasia of the pulmonary artery in the tetralogy of Fallot or hypoplasia of the arch of the aorta with coarctation). In other cases the operation was explorative as the investigations undertaken had not given sufficient definit information bout the inoperability of the condition, particularly in cases where multiple anomalies were present. In a ma nority of cases, incomplet preoperative diagnoses were concerned. As is pparent from Table 1 the mortality in persistent ductus arteriosus is no greater than when the operation is undertaken in older patients. The same holds true for palliative operations for the tetralogy of Fallot The mortality in coarctation of the aorta is,

TABLE 2 *Open cardiotomies with heart-lung machine (Carried out in Rigshosp Dept R) Congenital cardiac diseases Queen Louise s Children s Hospital 1958–1/5 1963*

A: Surgical repair accomplished.

		Age at operation			
		< 2 Yrs.		> 2 Yrs.	
	Total	Liv	Died	Liv	Died
Atrial septal defect	7			7	
Ventr septal defect					
Severe pulm. hyp.	2				2
Moderat pulm. hypertension	3			2	1
Valv pulm. stenosis	2	1		1	
Infund. pulm. stenos.	1			1	
Atrial septal defect and pulm. ten. with narrow valve ring	1	1			
Fallot's tetralogy	2			1	1
Aortico pulm. window	1			1	
Total anom. pulm venous return	1	1			
Cor triatriatum	1	1			
Total	21	4		12	4

4 Mths. old.

however considerably higher which is connected with the fact that the majority of these cases concern the juvenile type of coarctation where other anomalies were present simultaneously (O.A ") It should be oted in addition, that practically all of the infants who were submitted to operation under the age of 12 months were in such poor condition that it must be presumed that they belonged t the group of children with congenital heart diseases which experience has revealed would die if not submitted to operation.

II *Radical correction by pen" cardiotomy t t fancy*

In Department R, Rigshospitalet 111 open cardiotomies with employment of a heart-lung machine have been undertaken. Twenty six of these were undertaken on children from Queen Louise Hospital but only seven f these were infants (see Tables 2 and 3) as open cardiotomy was only undertaken in infancy if it was considered th t such an intervention was the only possibility and absolutely necessary In three out the seven cases, the anatomical conditio were so abnormal that correction was l possible (Table 3). In four cases (Table on the other hand, it proved possible correct the anomaly complet ly and all these children could be discharged in par cularly good condition.

A Gammelgaard Experiences with Ope tive Treatment of Steno-Fallot s Tetralo in Infants under th Age of Two Years

The investigation comprises 41 childr under the age of two years suffering fro the tetralogy of Steno-Fallot who were i vestigated in Queen Louise's Hospital 1955–59 The children comprised a grou of cases of the tetralogy of Steno-Fallot which pronounced cardia insufficiency w present. These cases were all submitted gio-cardiography because the clinical co ditions were considered to be so poor th operation was out of the question. Out

TABLE 3 *Open cardiotomies with heart-lung machine (Car l out in Rigsh ; l or R)*

B Surgical repair impracticable

	Total	Age a. peration			
		< 2 Yrs.		> 2 Yrs.	
		Liv	Died	Liv	Died
Single ventricle	1				1
Total anom. pulm. venous return	1		1		
Transposition	1				1
Partial persist truncus rteriosus	1		1[a]		
Atresia of the mit alve	1		1[b]		
Total	5		3		2

a 3 Mths. old.
b 4 Mths. old.

the children examined, operation was indicated in 26 while in 15 cases, on account of fewer symptoms and, in particular less severe ttacks of cyanosis, expectant treatment was employed in the hope that operation could be postponed until a more suitable time, at least until the age of two years. The 26 children in whom there were vital indications for operation, could be subdivided into two almost equally large groups. One group consisted of 12 children in whom operative treatment proved or was considered to be impossible for anatomical reasons. The majority of these children were under the age of six months and all of them died within nine months and all who were submitted to explorat ve thoracotomy died immediately after operation. Out of the 14 children submitted to palliative peration aorto-pulmonary hunt was established in 13 and a transpulmonary valvulotomy was undertaken in one case There was one post operative death. Follow up examination of the cases submitted t palliative operation when all of them were t least two years of age showed that half of the cases thrived well without further limitation of their normal activity and with only very slight cyanosis. In the other half the result were unsatisfactory and reoperation was considered but none of the patient were now in such danger as at the first operation Out of the 15 patients treated expectantl 11 proved at follow up examination to be thriving well while on the other hand four were so much worse that shunt operation was now considered to be indicated.

DISCUSSION

E Husfeldt May I supplement the information given by Gammelgaard and Therkelsen concerning the results of anastomotic operations on patient under the age of two years suffering from Steno-Fallot disease? I have information about the results obtained in older children and adults with anastomotic operations in Rigshospitalet These results will be published in "The Proceedings of the Royal Society of Medicine" W have operated upon very few children under the age of two years because these are collected in Queen Louise Hospital. Investigation and operation in these infants demands such special equipment and experience that they should be concentrated in a few centres. The result btained by Therkelsen and Gammelgaard belong to the best published. In Rigshospitalet we have recently concluded a follow-up investigation of 103

-atients submitted to operation for Steno-Fallot s disease during the years 1948–195., .o with a period of observation of 10-15 years. The operative mortality was 9 %. Seventy nine patients survived the anastomotic operation and 78 were followed up. Only four patients died during the period of observation, 5 9 11 and 12 years afte operation. One of these died from a brain abscess two from right sided cardiac failure and one patient died from unknown causes. Of the survivors, 40 patient (- 51 %) showed lasting improvement after operation as 17 had improved by two functional groups and .3 had improved by one functional group These results are of significance for decision concerning the age t which radical operation should be undertaken. We are unanimous that radical operation is the ideal solution but that the risk too great in operation on infants and it is also preferable if the heart has attained a certain degree of development before radical operation is undertaken. We are surely also unanimous that operation should not be under taken on small infants unless intervention is essential but that they should otherwise be left alone until radical operation can be undertaken under favourable conditions. By undertaking anastomotic operations on infants in poorest condition, the majority of children can survive until an age at which radical operation can be undertaken and some of them may even become so well that further intervention is scarcely indicated. The age at which radical operation should be undertaken is still a matter of disput Some surgeons favour 10–12 years while others consider that six years is a suitable age Time will reveal which is right

Torben Iversen, Copenhagen

BOOK REVIEWS

Eckerbek, Hans: Der Säugling. Physiologie, Pathologie und Therapie im ersten Lebensjahr

Springer Verlag. Berlin–Göttingen–Heidelberg, 1962. Price DM 89.60

The rapidly increasing interest in the diseases of the newborn is evident from the appearance of a number of textbooks relating to this topic. This book has concentrated on diseases of the newborn and during the first year of life. It is divided into the following sections: the physiology of the newborn and infants, feeding of newborn and infants, congenital malformations due to pre-natal factors and inborn errors of metabolism, birth trauma and neonatal complications, prematurity, nutritional disorders, and diseases of the respiratory tract, the circulatory system, the liver, the spleen, the kidneys and the endocrine glands, the nervous system, the skin, the skeleton, infectious diseases and vitamin deficiencies, and finally a section concerning drug therapy and prophylactic procedures. The author states in the preface that he has tried to combine the physiology of the newborn as seen from a clinician's point of view with a clinical textbook, and since the disorders in early life are so closely related to the normal development this is a very logical approach. In order to cover so much ground in 600 pages each section must consequently be very short, but the author has succeeded in collecting a vast amount of information in a clear and condensed form. Development in this field is very rapid and unfortunately it has not been possible to include some of the recent developments. For instance, the work of Apgar & Usher is not mentioned in relation to asphyxia of the neonatal and premature, the significance of Trisomia in other malformations than mongolism is not mentioned, as well as the importance of unconjugated or conjugated bilirubin in the etiology of kernicterus. A description of the exanthematous diseases (exanthema subitum, rubeola etc.) is also missing. The book includes references of which many are old, as a rule the author refers to the original papers when discussing syndromes or special clinical entities. A final objection is that the index is a little inadequate (cyanosis has no references!) but this is a very common drawback when one uses this kind of textbook in daily work. All these points are of minor importance and for everyday use the book has proven to be of great value for quick orientation. This is facilitated by many excellent illustrations, tables and figures.

Bent Friis-Hansen, Copenhagen

H. Hungerland und *J. Bredehl*: Kongenitale Störungen des Wasser- und Elektrolythaushaltes. Symposium Kassel Wilhelmshöhe.

182 pages, 83 fig. Springer Verlag, Berlin–Göttingen–Heidelberg 1962. DM 39.60.

Professor Hungerland, who is one of the editors of this book, is professor of pediatrics in Bonn and has been working for many years with problems related to water and electrolyte metabolism, and in 1961 he organized a symposium on congenital disturbances of water and electrolyte metabolism. These disturbances represent in a way nature's own experiment in human physiology and extensive studies of these cases are therefore of the greatest interest both from the clinical and the physiological point of view in spite of the fact that several of these diseases are very rare. The following subjects were dealt with: renal dysplasia and pyelonephritis, the congenital nephrotic syn-

drome, renal diabetes insipidus, congenital tubular insufficiencies, the de Toni Debré-Fanconi syndrome, hereditary nephritis, symptomatic diabetes insipidus, idiopathic hypercalcemia, congenital alcalosis with di arrhoea and finally different aspects of the electrolyte disturbances in patients suffering from fibrocystic disease of the pancreas and the adrenogenital syndrome The partici pants were mainly from Germany where the interest in these problems is of a later date The different papers are by and large good as they give a short and clear presentation of the often very complicated conditions found in these cases. The general objection to a book like this, consisting of papers presented at a symposium, is that not all papers are of the same standard, and some problems receive a very extensive discussion, whereas other equally important subjects are men tioned only briefly But here of course the skill of the chairman enters into the picture, and Professor Hungerland has been very successful in presenting a well balanced book, which will prove a useful, short introduction to these subjects, and a book which is unique in its kind.

Bent Friis-Hansen, Copenhagen

Intestinal B opsy ed. G.E.W Wolstenholme and Margaret P Cameron.

Ciba Foundation Study Group No. 14 in honour of Professor C Jiménez Diaz. J & A. Churchill, London, 1962. 1?0 pp. 53 ill.

This booklet records the May 1962 Ciba Symposium in Madrid and gives an excellent and well illustrated account of the findings in the intestinal mucosa in the various mal absorption syndromes. The paper on the dissecting microscope appearance of the mu cosa compared with the histologic pictures from the same areas (Both *et al.*) is of value, since it convinces the reader of the necessity of performing both stereomicroscopy and histologic examination for accurat diagnosis in malabsorption. Several papers are devoted to the pathogenesis of the mucosal changes; the effects of a gluten free diet are discussed and illustrated by Charlotte M. Anderson and R. R. W Townley of M l-bourne and by C. E. Rubin s group of Seattle. The changes in tropical sprue are described by Baker's group of Vellore South India. The very attractive book is concluded with a general discussion on methodology interpretation of results and topics for research. The reviewer finds the volume with its good illustrations and concise text an up-to-date book of reference for the pathologist and can also be recommended to the clinician interested in malabsorption.

Björn I Iversmark Stockholm

J J Mason Brown (ed): Surgery of Childhood.

Edward Arnold Ltd., London, 1962. 1300 pp Price £10

The extensive volume is the result of the contribution of 37 British authors. It deals with all problems in pediatric surgery some of which have been allowed to expand sur prisingly Thus, tuberculosis of the joints covers 75 pages, whereas only 48 are devoted to fractures, sprains, dislocations and epiphyseal injuries. In a text book on surgery the chapters on poliomyelitis and cerebral palsy are also rather extensive the latter covering 23 pages of which one deals with the surgical treatment. Some statements are not in agreement with Scandinavian routine e.g the operative treatment of intussusceptions and the definite condemnation of bone traction in the treatment of fractures. Most chapters are very well written and well-known and experienced authors give good reviews of their subjects. The references, however are extremely few for a text-book of this size.

N O Ericsson, Stockholm

Author index

Subject index